REMARKS

Claims 1-25 are pending in the application. Claims 14-17 have been withdrawn from consideration by the Examiner in view of a prior imposed restriction requirement.

New claims 18- 26 have been added, but they do not contain new matter. Support for the new claims is found in the specification at least at pages 8 and 9.

The Examiner has rejected claims 1-13 under 35 U.S.C. § 102 and/or § 103 based upon one or more of six, newly cited prior art references.

It is requested that the Examiner consider and make of record the reference cited in the IDS filed by applicant on March 13, 2003. It is also requested that the Examiner provide a copy of the initialed form PTO SB/08A to the applicant with the next communication.

In Paper No. 20, the Examiner has stated that she considers the restriction requirement issued in the Office Action mailed August 19, 2002. First, this is not correct. The Office Action makes clear that the claims 14-17 are withdrawn as reciting non-elected species of drugs.

Moreover, assuming *arguendo*, the Examiner was asserting that claims 14-17 were drawn to a non-elected invention, the applicant traverses the imposition of a restriction requirement as it is improper. As there is a generic linking claim, there is no basis for a finding that the each of the recited species of claims 14-17 is an independent invention, and notably, the Examiner has failed to articulate one, as required by the M.P.E.P. See M.P.E.P. 808.01. Accordingly, the applicant requests withdrawal of the restriction requirement.

Finally, the applicant thanks the Examiner for clarifying her position with respect to the to Kelm references (Kelm '105 and Kelm '290), and respectfully request that in future, care is taken to unambiguously identify all cited art, particularly in cases where the patents name the same inventor.

I. Rejection Under 35 U.S.C. § 102(e) Based Upon WO 94/09745.

The Examiner has rejected claim 1 under 35 U.S.C. § 102(e) as being anticipated by WO 94/09745 of Rashid, *et al.* ("Rashid"). As basis for the rejection, the Examiner asserts that Rashid teaches a controlled release capsule of a starch that is coated with a solution of polyvinyl chloride, polyvinyl acetate copolymer, or an ethyl cellulose solution. The capsule is filled with a

pharmaceutical active agent that is released into the patient's "gastrointestinal tract" within two to ten hours of oral administration.

The applicant respectfully traverses this rejection.

Rashid teaches a capsule comprising a male plug formed of a water swellable hydrogel and a female body (also referred to as the "capsule body"). The body includes a flared mouth portion adjacent to a neck portion. The female body of the capsule of Rashid may be constructed from numerous types of polymers. Alternatively, Rashid teaches that the female body may be a water soluble material having a coating, such as a gelatin or starch capsule body coated with a solution of polyvinyl chloride, a polyvinyl acetate copolymer, or an ethylcellulose solution. The male plug that comprises the second portion of controlled release capsule of Rashid is constructed of a hydrogel, but is not provided with a coating.

Rashid teaches that upon oral administration in the aqueous environment of the "gastrointestinal tract," the cap on the male potion quickly dissolves, causing absorption of water into the hydrogel male plug. It swells, and is expelled from the body of the capsule after a "predetermined time interval (for example two to ten hours)." Rashid at 7. By this means, the contents of the Rashid device are released into the "patient's gastrointestinal tract."

In contrast, the invention is directed to a drug delivery composition including a starch capsule that contains a drug and which is coated with a coating such that the drug is predominantly released from the capsule in the <u>colon or terminal ileum</u>.

Rashid does not teach or suggest each element of the invention as claimed. First, the controlled release capsule of Rashid is not a starch capsule, rather, it is a controlled release capsule of two distinct parts: one portion that is a hydrogel (male plug), and one portion that is not a hydrogel, and can instead be a polyethylene, polypropylene, poly (methyl methacrylate), polyvinyl chloride, polystyrene, polyurethane, polytetrofluoroethlyene, nylon, polyformaldehyde, polyester, cellulose acetate, nitrocellulose, or a starch or gelatin capsule coated with polyvinyl chloride, polyvinyl acetate copolymer or ethyl cellulose solution. Thus, Rashid does not provide a teaching of a capsule that is (1) *entirely* formed of starch, and (2) coated throughout with a coating such that the drug is predominantly released from the capsule in the colon and/or the terminal ileum.

Additionally, there is no teaching in Rashid that the coating which may be present on the female portion of the two-part Rashid capsule is a coating that facilitates the predominant release

of the drug from the capsule into the colon or terminal ileum. Rashid teaches that the drug in the Rashid two part capsule is released in the "gastrointestinal tract." As is known to a person of skill in the art, the "gastrointestinal tract" includes the stomach, the small intestine (including the duodenum the jejunum and the ileum), the large intestine (including the caecum and the vermiform appendix) and the colon (including the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum). See, Gray's Anatomy (36th British Ed.) – Williams and Warwick (1980) at 1333-1357 (attached hereto). Thus, there is no specific teaching or suggestion in Rashid that the hydrogel, which begins to swell as soon as it comes in contact with water after oral administration, delivers the drug to the colonic region, and/or contains a coating such that the drug is predominantly released from the capsule in the colon and/or terminal ileum.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the § 102 rejection based upon Rashid.

II. Rejection Under 35 U.S.C. § 102 (e) Based Upon U.S. Patent No. 5,622,721.

The Examiner has rejected claims 1, 2, 5-7, 9, 10 and 12 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,622,721 of Dansereau, et al. ("Dansereau"). According to the Examiner, Dansereau teaches an enteric-coated oral dosage form, wherein the release of the active agent is to the "lower gastrointestinal tract." The dosage form of Dansereau, according to the Examiner, can be an enteric-coated starch or gelatin capsule including polymers or copolymers that dissolve at a pH of 5.5 or above.

The applicant respectfully traverses this rejection.

Dansereau teaches a novel enteric-coated oral dosage form of a risedronate active ingredient. Dansereau teaches that the coatings of the dosage form are limited to <u>enteric</u> coatings. Col. 12, lns. 34-48; Col. 13, lns. 34-47. Dansereau teaches that this enteric coating may be applied to "a compressed tablet, a gelatin capsule, and/or the beads, granules, or particles of risedronate which are encapsulated into starch or gelatin capsules or compressed into tablets." Throughout Dansereau, the enteric coating is described as one that will prohibit the undesirable delivery of the risedronate active ingredient to the mucosal and epithelial tissues of the upper gastrointestinal tract thereby releasing the drug in the "lower gastrointestinal tract," which is expressly defined by Dansereau as being "the small intestine and the large intestine." Col. 4, lines 64-65. However, as discussed above, non-specific disclosure of the release in the "lower

gastrointestinal tract," is not necessarily indicative of a coating prepared such that the drug is released in the terminal ileum or colon. See Col. 7, lns. 6-9.

Dansereau does not teach each element of the claims as the oral dosage form of Dansereau is not provided with a coating such that the drug is predominantly released in the terminal ileum or colon. In fact, the opposite is true. A simple enteric coating does not provide colonic release, since it necessarily delivers the drug to the upper small intestine, as evidenced by the pharmacopeal tests that are designed to ensure such delivery. As can be seen from the standards set forth by the U.S. Pharmacopoeia, enteric coated articles need only to remain intact for two hours at acidic pH and subsequently demonstrate drug release after 45 minutes at pH 6.8 See, U.S. Pharmacopoeia General Drug Release Standard (Enteric Coated Articles) at 1795-96 (attached hereto).

In contrast, for a coated capsule to reach the terminal ileum/colon, it is essential to provide a coating that will remain intact for a period typically of at least three hours under the pH conditions present in the small intestine, as it is known that it takes this long for a capsule to move from the duodenum to the terminal ileum. See Davis, Chapter 4 in "Drug Deliver to the Gastrointestinal Tract," Hardy *et al.*, eds. (Ellis Horwood Ltd., Halston Press 1989) (attached hereto)). Thus, an "enteric coating" as described by Dansereau is not the same as the claimed coating provided to the starch capsule of the claimed drug delivery composition.

Accordingly, for at least these reasons, it is respectfully requested that the Examiner reconsider and withdraw the rejection based upon Dansereau.

III. Rejection Under 35 U.S.C. § 102(e) Based Upon U.S. Patent No. 5,656,290.

The Examiner has maintained the rejection of claims 1-13 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,656,290 of Kelm, *et al.* ("Kelm"). The Examiner continues to rely on the § 102(e) date of Kelm for <u>all</u> of its disclosures, and asserts that Kelm teaches a pharmaceutical dosage form for colonic delivery that comprises a drug encapsulated in a hard capsule that may be a starch or gelatin capsule, and which is coated with a coating that is a copolymer of methacrylic acid methyl methacrylate, or cellulose derivative.

The applicant continues to traverse the rejection.

Kelm patent claims priority as a continuation in part to prior filed application Ser. No. 279,361 ("the '361 application"), filed July 22, 1994, which in turn claims priority as a continuation application to serial no. 23,412 ("the '412 application"), filed February 26, 1993.

This application has an effective filing date of June 21, 1994. In order to constitute anticipatory prior art against the claims of this application under 25 U.S.C. § 102(e), all elements of the invention must have been disclosed in the chain of applications that gave rise to Kelm '290 prior to June 21, 1994.

Applicant respectfully submits that Kelm does not anticipate the pending claims. Although the issued Kelm patent discloses a starch capsule, the priority applications do not. The parent '361 application fails to disclose the use of starch capsules, as evidenced by U.S. Patent No. 5,670,158 of Davis ("Davis"). Davis issued from U.S. serial no. 558,338, filed November 15, 1995, which itself is a § 120 continuation of the '361 application and therefore shares an *identical* disclosure. Davis does not disclose use of starch capsules, a point the Examiner concedes. See Paper No. 20 at 4. The '361 application must also fail to disclose starch capsules, as Davis is a continuation application, and the addition of new matter to a continuation application is prohibited. *See* 35 U.S.C. § 120. Similarly, the '412 application must not disclose a starch capsule, because the '361 application is also a § 120 continuation of the '412 application, and therefore must have the identical disclosure.

Accordingly, the subject matter related to the starch capsule was, at minimum, subject matter disclosed only at the actual date of the filing of the application that became Kelm (May 17, 1995), well after the effective date of this application.

For at least these reasons, the disclosure of Kelm that is proper § 102(e) prior art with respect to the present application does not disclose all elements of the claims, and is not anticipatory.

IV. Rejection Under 35 U.S.C. § 103 Based Upon U.S. Patent No. 5,670,158 Combined with U.S. Patent No. 5,342,624.

The Examiner has maintained the rejection of claims 1-13 under 35 U.S.C. § 103(a) as being unpatentable over the disclosure of U.S. Patent No. 5,670,158 of Davis, *et al.* ("Davis") taken in combination with the disclosure of U.S. Patent No. 5,342,624 of McNeill, *et al.* ("McNeill"). The Examiner contends that Davis teaches pharmaceutical dosage forms for colonic delivery comprising drugs encapsulated in an enteric coated capsule, which enteric coating comprises a pH sensitive material that will dissolve at a pH of above 5. The Examiner concedes that Davis does not teach a starch capsule.

The Examiner attempts to fill this void by asserting McNeill, which she contends teaches that "hard gelatin capsule or starch capsules are a conventional class of capsules." The Examiner reasons that the gelatin capsule and starch capsule are "substantially equivalent," and, therefore, it would have been obvious for one of ordinary skill in the art to use the starch capsule of Davis in the composition of McNeill.

The applicant respectfully traverses the rejection.

Davis discloses a dosage unit form of a composition that comprises two parts: (1) a rapidly dissolving bisacodyl means; and (2) a delivery means that delays the release of bisacodyl until the dosage form has been transported to a specific point in the gastrointestinal tract. Davis teaches that delivery means include tablets or capsules, but does not specify use of starch capsules, instead describing pulse capsules and hard and soft gelatin capsules. The invention of Davis is directed to rapid, targeted delivery of the bisacodyl means to facilitate maximal laxation and reduced absorption, thereby reducing occurrences of secondary diarrhea. The Examiner concedes that Davis does not teach a starch capsule as a delivery means.

McNeill teaches a device for the controlled release of an active material that is formed from at least two interpenetrating pieces. The device may be a capsule containing an active material where the capsule is formed from a male portion and a female piece. The male portion is made of a material that is water swellable, and therefore swells upon contact with water so as to disengage from the female piece and release the active material. McNeill teaches that a preferred construction of the female piece of the device may be a capsule that is coated with specific materials. Col. 6, lns. 1-30. McNeill teaches that <u>this portion</u> of the device may be made of a conventional hard gelatin or starch coated with a specific solution of certain polymers. Col. 6, lns. 17-21. McNeill does not teach, as the Examiner asserts, that hard gelatin capsules and starch capsules are a "conventional class of capsules," nor does it teach that such capsules are "substantially equivalent." At minimum, McNeill teaches that, in the eyes of Messrs. McNeill and Stevens, the inventors, hard gelatin or starch capsules are preferred for use in the specific application of McNeill. Such teaching is <u>not</u> a generalized teaching to those skilled in the art that the capsules are substantially equivalent.

The Examiner has failed to meet all necessary elements to establish a *prima facie* case of obviousness based upon the combination of Davis and McNeill. Davis, as conceded by the Examiner, does not teach or suggest use of a starch capsule. McNeill does not remedy this

deficiency, as it teaches only a device formed from at least two interpenetrating pieces where one portion of the entire device is a gelatin or a starch capsule having a specific coating and the other portion is a hydrogel. There is no teaching in McNeill that the entire device bears a coating, or that the entire device is made of a starch capsule.

Further, the Examiner has failed to demonstrate a motivation or provocation in the prior art references that would have caused a person of skill to make the suggested combination. The teachings of McNeill do not establish that a starch capsule and a gelatin capsule are an art-recognized "class" or "category" of capsules. Rather, McNeill discloses only that starch and gelatin capsules may be preferred by the inventors of the McNeill device for use in that very specific two part McNeill drug delivery device. Such teaching is not evidence of the art – recognized substantial equivalence of the two differing capsules.

Moreover, the device taught in McNeill includes two parts, only one of which is made of starch. The other is a hydrogel. This difference creates a drug delay mechanism that is different than that of the present invention. The McNeill delay relies on the architecture of the delivery device (one portion of which is a swellable material and "pops" off upon contact with water). The invention relies on a starch capsule provided with a coating such that the drug is predominantly released from the capsule in the colon or terminal ileum by the dissolution of the coating when it reaches the targeted area. A person of skill in the art would have had no reason to substitute the female piece starch capsule of McNeill in the compositions of Davis, as there is no teaching, or suggestion in either of the references that use of a starch capsule would be suitable for use as the Davis dosage form. In addition, substitution of the open ended female piece of McNeill would render the Davis device ineffective, for the bisacodyl compound would leak out prior to the target site hindering the Davis objective of maximal laxation with minimal absorption. Given such deficiencies, a person of skill in the art would have had no reasonable expectation that the combination would be successful.

Thus, the combination suggested by the Examiner does not teach or suggest the invention. It is requested that the Examiner reconsider and withdraw the rejection.

V. Rejection Under 35 U.S.C. § 103(a) Based Upon Davis and U.S. Patent No. 5,672,359.

The Examiner has rejected claims 1-13 under 35 U.S.C. § 103 based upon the combination of Davis with U.S. Patent No. 5,672,359 of Digenis, *et al.* ("Digenis"). As basis for

the rejection, Davis is applied in the same manner as in the prior § 103 rejection. The Examiner uses Digenis for its alleged teaching of coated hard capsules made from gelatin or starch suitable for colonic delivery of peptide drugs such as vaccines and proteins. The Examiner reasons that it would have been obvious for one of skill in the art to optimize Davis' capsule using the starch capsule in view of the teaching of Digenis that "hard gelatin capsule can be gelatin or starch or hydrophilic." The applicant respectfully traverses the rejection.

The disclosure of Davis is described *supra* (Section IV) and is relied upon herein.

Digenis teaches a multi-compartment hard capsule with controlled release properties that may be made from a material such as gelatin, starch, or a hydrophilic polymer. In an embodiment, the Digenis multi-compartment hard capsule can be used to deliver, *e.g.*, peptide drugs to the colon. The capsule of Digenis includes at least one inner compartment, at least one intermediate compartment surrounding the at least one inner compartment, and at least one outer compartment surrounding the at least one intermediate compartment, and each compartment comprises at least one drug component or active agent. Using the Digenis multi-compartment capsule, the step-wise delivery or sequential delivery of several drugs is achieved as a function of the combination of the physical properties of the materials that constitute the individual compartments. Thus, Digenis teaches that the drug delivery system described therein possesses the ability to deliver a desired drug or combination of drugs within seconds to hours after administration by release from the outer compartment.

The Examiner has failed to establish a *prima facie* case of obviousness based upon the combination of Davis and Digenis. Davis concerned with the rapid and targeted delivery of bisacodyl compound in order to optimize maximum laxation and reduced absorption, thereby mitigating secondary diarrhea. A person of skill in the art would not have been motivated to combine the teachings of Davis with those of Digenis, which are directed to a step-wise delivery of three or more drugs over a period of time from seconds to hours. Given the disparate objectives of each of the references, a person of skill in the art would not have made the combination of Davis and Digenis, nor would he have expected that the combination would give rise to a successful drug delivery capsule, as is presently claimed.

Accordingly, for at least these reasons, it is respectfully requested that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

VI. Rejection Under 35 U.S.C. § 103(a) Based Upon Rashid Combined With Dansereau.

The Examiner has rejected claims 2-10 and 12 under 35 U.S.C. § 103(a) as being unpatentable over the disclosure of Rashid, taken in view of that of Dansereau. The Examiner relies upon Rashid as applied in a prior rejection, but concedes that Rashid does not teach the coating materials as claimed. The Examiner asserts that Dansereau teaches "enteric-coated oral dosage form" wherein the release of the active agent is to the lower gastrointestinal tract, and includes such coatings as polymers or copolymers that dissolve at a pH of 5.5 or above, *e.g.*, Eudragit, or methacrylic acid polymer-copolymer. Thus, the Examiner reasons that it would have been obvious for one of ordinary skill in the art to optimize the coating of Rashid using the coating materials in view of the teaching of Dansereau, because the references "recognize the advantageous results in the use of delay coating materials suitable to coat starch capsules or to release active agent into the intestinal tract."

The applicant respectfully traverses this rejection.

The disclosures of Rashid and Dansereau are discussed *supra* (Sections I and II), and are relied upon herein.

Based upon the combination of Rashid and Dansereau, the Examiner has failed to establish a *prima facie* case of obviousness. First, the combination of Rashid and Dansereau does not teach or suggest all elements of the invention. As discussed above, neither Rashid nor Dansereau disclose a coating such that the drug is predominantly released from the capsule in the colon and/or the terminal ileum (see discussion in section II). Specifically, the general disclosure of Dansereau of an enteric coating does not necessarily require that the coating is formulated for delivery to the colon or terminal ileum. The disclosure of Rashid does not remedy this deficiency, for, as discussed *supra,* Rashid discloses only a drug delivery system that is capable of delivery to the "gastrointestinal tract," which in itself is not indicative that the delivery is targeted to the colon and/or terminal ileum.

Additionally, a person of skill in the art would not have been motivated to make the combination of Rashid and Dansereau. Combination of the open-ended starch female body of Rashid with the device of Dansereau would negate the objective of Dansereau, to avoid exposure of the tissues of the upper gastrointestinal tract to risedronate, for the open ended capsule would prematurely release the risedronate. For at least these reasons, no motivation to combine is

present and no reasonable expectation of success would have been present in the mind of a person of skill.

Accordingly, for at least the reasons given above, it is respectfully requested that the Examiner reconsider and withdraw the rejection based upon the combination of Rashid and Dansereau.

CONCLUSION

In view of the foregoing, it is respectfully submitted that claims 1-13 are fully patentable over the cited prior art. Reconsideration and allowance of the claims at the earliest opportunity is respectfully requested.

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23 october 2003 By: Kristyne A. Bullock

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Enclosures:

- Petition for Three Month Extension of Time
- Gray's Anatomy (36th British ed.) Williams and Warwick (1980) at 1333-1357.
- U.S. Pharmacopoeia General Drug Release Standard (Enteric Coated Articles) at 1795-96.
- Davis, Chapter 4 in "Drug Deliver to the Gastrointestinal Tract," Hardy *et al.*, eds. (Ellis Horwood Ltd., Halston Press 1989).

GRAY'S ANATOMY

36th Edition

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PHILADELPHIA

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1980

peritoneum in the subphrenic region has a greater absorptive capacity than the other regions; hence inflammatory products, if they gained access to this region, would more rapidly pass into the general circulation. It was held by some that in the subphrenic region there were gaps (peritoneal stomata) between the mesothelial cells lining the peritoneum and similar gaps (endothelial stigmata) between the endothelial cells lining the lymph vessels subjacent to the peritoneum, and that these gaps greatly facilitated absorption. It is now generally believed that these gaps are artefacts produced during the histological technique employed to demonstrate them, that absorption is more or less equally rapid in all parts of the peritoneum, and that the greater absorption in the upper part of the abdomen is to be correlated partly with the larger area of the peritoneal surface in the subphrenic region and partly with the fact that respiratory movements expedite absorption in this zone.

PERITONEAL STRUCTURE

The peritoneum consists of a single layer of flattened mesothelial cells which covers a layer of loose connective tissue. In most areas the mesothelium forms a continuous surface. Adjacent mesothelial cells are joined by junctional complexes, which probably allow the passage of macrophages to and from the underlying connective tissue, in the same manner as endothelial cell junctions allow leucocytes to pass from the bloodstream. In other areas, however, as in the greater omentum, the peritoneum may be discontinuous, presenting a series of fenestrations which may be visible to the unaided eye. At such points the mesothelial surface layer is continuous over the trabeculae of connective tissue which interlace around the margins of the fenestrae.

The sub-mesothelial connective tissue carries the cells usually found in loose connective tissues, but the population of macrophages, lymphocytes, and in some regions adipocytes, are particularly numerous. Aggregations of lymphocytes occur in some regions and form macroscopic 'milky spots' under the mesothelium. It has been claimed that the mesothelial cells possess a phagocytic capacity, and that they may leave the surface to form free macrophages. They may also transform into fibroblasts, and fusion between layers of fibroblasts of mesothelial origin may lead to macroscopic adhesions between the peritoneal surfaces of adjacent structures; if extensive, these may have serious clinical consequences, interfering with intestinal motility, or even leading to complete obstruction of the gut.

The mesothelium is similar in many respects to the endothelial lining of blood vessels, in that it forms a dialysing membrane across which fluids and small molecules of various solutes may pass. Numerous pinocytotic vesicles are present near the cell surfaces, the remaining cytoplasm being relatively poorly provided with organelles, indicating a low level of metabolic activity (Tesi and Forssmann 1970). Normally, small volumes of fluid are transferred across the peritoneal surfaces. Therapeutically, however, considerable volumes of fluid may be administered via the intraperitoneal route, whilst conversely, certain blood-borne substances such as urea can be dialysed from the bloodstream into fluid artificially circulated through the peritoneal cavity.

PERITONEAL FLUID

The fluid layer which covers the peritoneal surfaces, as already stated, contains water, electrolytes and other solutes derived from the interstitial fluid of the neighbouring tissue and from the plasma of adjacent blood vessels. It also contains proteins and a variety of cell types (Carr 1967). The latter vary in their numbers, structure and type in different pathological conditions, and they are hence of diagnostic importance. Normally the cells consist of desquamated flat mesothelial elements derived from the peritoneal surfaces, and of wandering macrophages, mast cells, fibroblasts, lymphocytes and small numbers of other leucocytes. Some of these cells, particularly the macrophages, can migrate freely between the peritoneal cavity and the surrounding connective tissue; particulate material injected intraperitoneally may therefore be ingested by these cells and transported to various other sites in the body. The lymphocytes in the fluid provide both cellular and humoral immunological defence mechanisms.

PERITONEAL VESSELS AND NERVES

The parietal and visceral layers of the peritoneum are respectively developed from the somatopleural and splanchnopleural layers of the lateral plate mesoderm (p. 118). Correlated with their embryological origin is the fact that the parietal peritoneum derives its arterial supply from the somatic (body wall) arteries supplying the abdominal and pelvic walls; its veins join the systemic veins in the neighbouring parts of the body wall, its lymphatics also join those in the body wall and thus drain into parietal lymph nodes, and its nerve supply is derived from the spinal nerves which also supply the muscles and skin of the parietes. The visceral peritoneum, however, which is to be considered as an integral part of the viscera themselves, derives its arterial supply from the arteries supplying the appropriate viscera, its veins and lymphatics join the visceral veins and lymph vessels, and its nerve supply is derived from the autonomic nerves innervating the viscera. The difference in the sensibility of the two layers of the peritoneum is thus to be correlated with their different innervation. Whereas pain is elicited by the application of tactile, thermal or chemical stimuli to the parietal peritoneum (in the conscious patient), these stimuli are ineffectual when applied to the visceral peritoneum (or to the viscera themselves). For example, the liver, stomach or intestine can be cut, pinched, clamped or burned in the conscious subject without evoking pain, the insensibility of the alimentary canal to these forms of stimulation extending from about the middle of the oesophagus down to the junction of the endodermal and ectodermal parts of the anal canal. On the other hand, a stimulus which evokes pain when applied to viscera or visceral peritoneum is tension, such as that accompanying over-distension of the hollow viscera or traction on the mesenteries, which stretches the nerve plexuses in the walls of the organs or the nerves in the mesenteries. Other effective stimuli are spasm of visceral muscle, and ischaemia (deprivation of blood supply). The somatic nerves which supply the parietal peritoneum also supply the corresponding segmental area of skin and trunk muscles, and in cases where the parietal peritoneum is irritated, the muscles are reflexly contracted, thus causing rigidity of the abdominal wall in that region. The parietal peritoneum of the under surface of the diaphragm is supplied centrally by both phrenic nerves and peripherally by the lower six intercostal and the subcostal nerves. Irritation of the peripheral part of the diaphragmatic peritoneum may result in pain, in tenderness and muscular rigidity in the area of distribution of the lower intercostal nerves. On the other hand, irritation of the peritoneum over the central portion of the diaphragm may result in pain in the area of distribution of the cutaneous branches of the third, fourth and fifth cervical nerves over the shoulder region and can lead to diagnostic errors.

The Stomach

The stomach (ventriculus or gaster) is the most dilated part of the alimentary canal, and is situated between the end of the oesophagus and the beginning of the small intestine. It lies in the epigastric, umbilical, and left hypochondriac regions of the abdomen, and occupies a recess bounded by the upper abdominal viscera, and completed in front and on the left side by the anterior abdominal wall and the diaphragm. Its shape and position are modified by changes within itself and the surrounding viscera, and no one form or position is typical. Its mean capacity varies with age, being about 30 ml at birth, increasing gradually to about 1000 ml at puberty, and commonly reaching to about 1500 ml in the adult.

The stomach has two openings, and is described as if it had two borders or curvatures, and two surfaces. In reality, of course, its external surface is a continuum, and it is not divided by any readily perceptible 'borders'. Since, however, the peritoneal surface is interrupted by the attachments of the greater and lesser omenta, along profiles which define the gastric shadow in

radiographs, these 'borders' or curvatures may be conveniently regarded as separating the surfaces. (Similar arbitrary borders are assigned to the heart, see p. 639.)

THE GASTRIC ORIFICES

The opening by which the oesophagus communicates with the stomach is the *cardiac orifice*, and is situated on the left of the median plane, behind the seventh costal cartilage 2·5 cm (1 in.) from its junction with the sternum, and at the level of the eleventh thoracic vertebra. It is placed about 10 cm (4 in.) from the anterior abdominal wall and is 40 cm (16 in.) from the incisor teeth. The short abdominal part of the oesophagus is like a truncated cone and curves sharply left, the base of the cone being continuous with the cardiac orifice of the stomach. The right side of the oesophagus is continuous with the lesser curvature of the stomach, while the left side joins the greater curvature at an acute angle, termed the *cardiac notch*. The part of the stomach to the left of and above the cardiac orifice is called the *fundus*—a curiously inappropriate term, but it is the *bottom* of the stomach, if entered surgically from below.

The opening into the duodenum is the *pyloric orifice*, and its position is usually indicated (**8**.103) by a circular groove on the surface of the organ, termed the *pyloric constriction*, which indicates the position of the pyloric sphincter. In the living subject, at operation, it can be identified by the prepyloric vein, which runs vertically across its anterior surface. The pyloric orifice lies about 1·2 cm (0·5 in.) to the right of the median plane near the level of the lower border of the first lumbar vertebra (transpyloric plane), when the body is in the supine position and the stomach is empty.

THE GASTRIC CURVATURES

The lesser curvature, extending between the cardiac and pyloric orifices, forms the right (or posterosuperior border) of the stomach. It descends as a continuation of the right margin of the oesophagus in front of the decussating fibres of the right crus of the diaphragm, and then, turning to the right, it curves below the omental tuberosity of the pancreas and ends at the pylorus (**8**.103, 105). The most dependent part of the curve may form a notch, named the *angular incisure*, which varies somewhat in position with the state of distension of the viscus; it may be used to separate the stomach into right and left parts. The lesser curvature gives attachment to the lesser omentum, the two layers of which contain the right and left gastric vessels, adjacent to the lesser curvature.

The greater curvature is directed antero-inferiorly, and is four or five times as long as the lesser curvature. Starting from the cardiac orifice at the cardiac notch, it forms an arch backwards, upwards, and to the left; the highest point of the convexity (of the *fundus*) is on a level with the left fifth intercostal space and lies just below the left nipple, though this level, like that of the diaphragm, varies with the phases of respiration (*see* pp. 550–551). From this level it may be followed downwards and forwards, with a slight convexity to the left almost as low as the cartilage of the tenth rib, when the body is in the supine position; it then turns to the right, to end at the pylorus. Directly opposite the angular incisure of the lesser curvature the greater curvature presents a bulge, which is the left extremity of the *pyloric part* of the stomach; this is limited on the right by a slight groove, which indicates the subdivision of the pyloric part into a pyloric antrum and a pyloric canal. The latter is only 2 to 3 cm in length and terminates at the pyloric constriction. At its commencement the greater curvature is covered by peritoneum continuous with that on the front of the stomach. On the left side of the fundus and the adjoining part of the body, the greater curvature gives attachment to the gastrosplenic ligament, while to its lower region are attached the two layers of the greater omentum, separated from each other by the gastro-epiploic vessels. The gastrosplenic ligament and the greater omentum (together with the gastrophrenic and lienorenal ligaments, *see* pp. 1324, 1326) are directly continuous, being parts of the original dorsal mesentery of the stomach (dorsal mesogastrium) (p. 205). The separate names merely indicate regions of the same peritoneal fold.

THE GASTRIC SURFACES

When the stomach is empty and its walls contracted, its surfaces are almost superior and inferior, but when it is distended they become anterior and posterior respectively. They may therefore be described as anterosuperior and posterio-inferior.

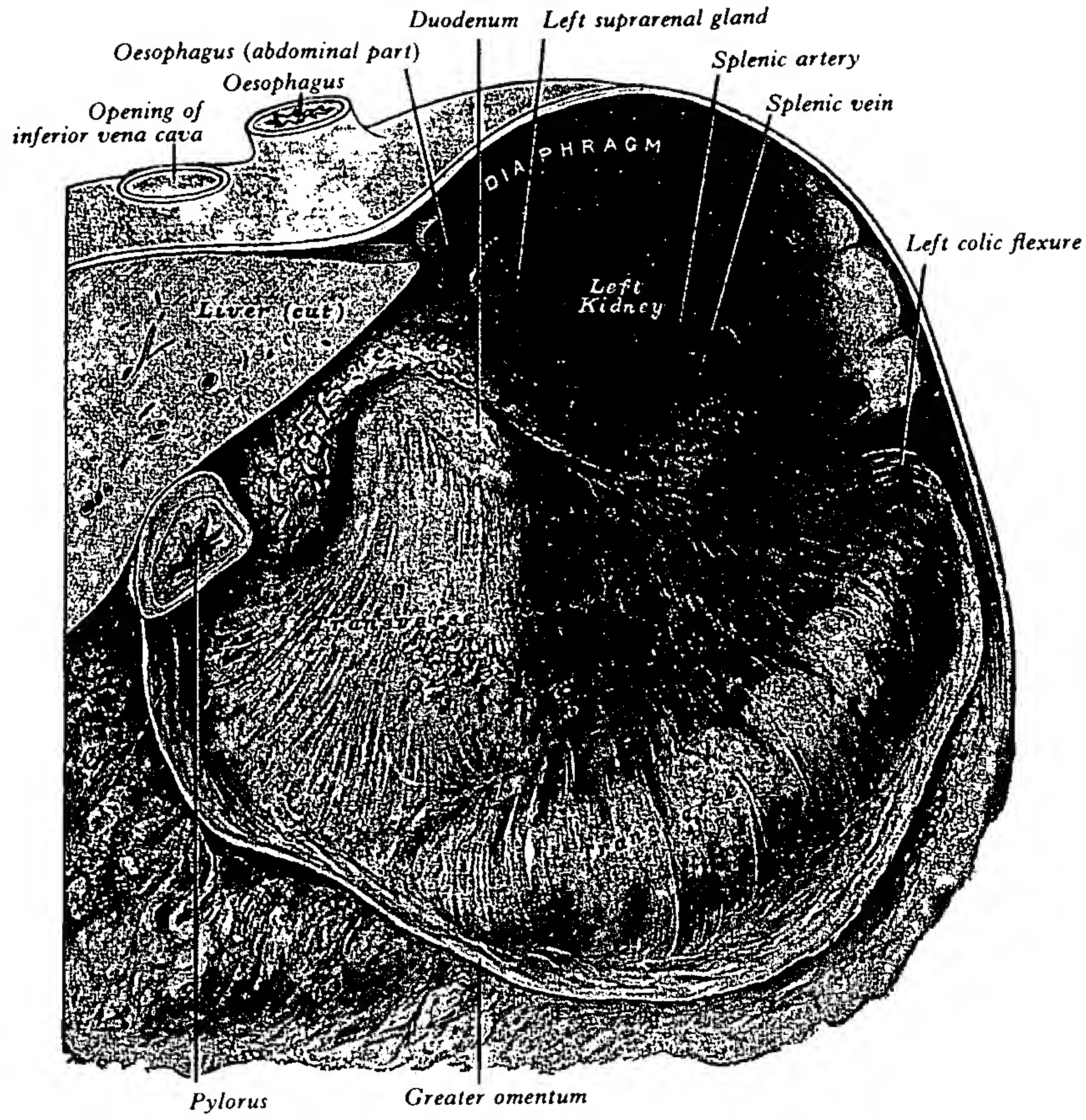
Anterosuperior surface. The left part of this surface is posterior to the left costal margin. It is in contact with the diaphragm, which separates it from the left pleura, the base of the left lung, the pericardium, and the sixth, seventh, eighth and ninth ribs and intercostal spaces of the left side. It is related to the costal attachment of the upper fibres of origin of the transversus abdominis, which intervene between it and the seventh, eighth and ninth costal cartilages. The upper and left part of this surface becomes posterolateral and is in contact with the gastric surface of the spleen. The right half is in relation with the left and quadrate lobes of the liver and with the anterior abdominal wall. When the stomach is empty, the transverse colon may lie on the front of this surface. The whole surface is covered with peritoneum, and a part of the greater sac of the peritoneum intervenes between it and the above structures.

Postero-inferior surface. This is related to the diaphragm, the left suprarenal gland, the upper part of the front of the left kidney, the splenic artery, the anterior surface of the pancreas, the left colic flexure, and the upper layer of the transverse mesocolon. These structures form the shallow *stomach bed*, (**8**.104), but the stomach is separable from them, and can slide over them, due to the intervening omental bursa (lesser sac). The gastric surface of the spleen is also generally described as part of the stomach bed, but as stated above it is separated from the stomach by a part of the greater sac. Further, the greater omentum and the transverse mesocolon separate the stomach from the duodenojejunal flexure and small intestine. The postero-inferior surface is covered with peritoneum, except near the cardiac orifice, where there is a small, somewhat triangular area, in direct contact with the left crus of the diaphragm, and sometimes with the left suprarenal gland. The left gastric vessels reach the lesser curvature of the stomach at the right extremity of this area (in the left gastropancreatic fold, p. 1326), and from its left side a short peritoneal fold, termed the *gastrophrenic ligament*, which is continuous below with the lienorenal and gastrosplenic ligaments, passes to the inferior surface of the diaphragm.

A plane passing through the angular incisure on the lesser curvature and the left limit of the opposed bulge on the greater curvature divides the stomach into a large, left portion or *body* and a small, right, or *pyloric part*.

Radiology

By means of X-rays the form and position of the stomach can be studied in the living subject after swallowing a suitable 'meal' containing barium sulphate (**8**.108). During the process of digestion, it is divided by a muscular constriction into a large, dilated, left region, and a narrow, contracted, tubular, right portion. The constriction is in the body of the stomach, and does not follow any of the anatomical landmarks; indeed, it shifts gradually towards the left as digestion progresses. The position of the stomach varies with the posture, with the amount of the stomach contents and with the condition of the intestines on which it rests. It is also influenced by the tone of the abdominal muscle and of the musculature of the organ itself, and by the type of body build of the individual. In the commonest type of stomach, the empty organ is somewhat J-shaped and, in the erect posture, the pylorus descends to the level of the second or the upper part of the third lumbar vertebra, and the most dependent part of the stomach is below the level of the umbilicus. The fundus is usually distended with gas. Variation in the amount of its contents affects mainly the body of the stomach, the pyloric portion remaining in a more or less contracted condition during the process of digestion. As the stomach fills it tends to expand forwards and downwards in the direction of least resistance, but when this is interfered with by a distended condition of the colon or intestines the fundus presses upwards on the liver and diaphragm and gives rise to the feelings of oppression and palpitation complained of in such cases. When hardened ***in situ***



8.104 The stomach bed: a dissection in which the stomach has been removed to show its posterior relations.

the contracted stomach is crescentic, the fundus looking directly backwards. The surfaces are superior and inferior, the upper having, however, a gradual downward slope to the right. The greater curvature is in front of and at a slightly higher level than the lesser.

The position of the full stomach depends, as already indicated, on the state of the intestines: when the latter are empty the fundus expands vertically and also forwards, the pylorus is displaced towards the right, and the whole organ assumes an oblique position, so that its surfaces are directed more forwards and backwards. The lowest part of the stomach is at the pyloric antrum, which reaches below the umbilicus. Where the intestines interfere with the downward expansion of the fundus the stomach retains the horizontal position which is characteristic of the contracted viscus. Less commonly the stomach may lie almost transversely, even in the erect posture; this is known as the '*steer-horn*' type of stomach. Intermediate types of stomach, between the J-shaped and 'steer-horn' varieties, also occur (Barclay 1936).

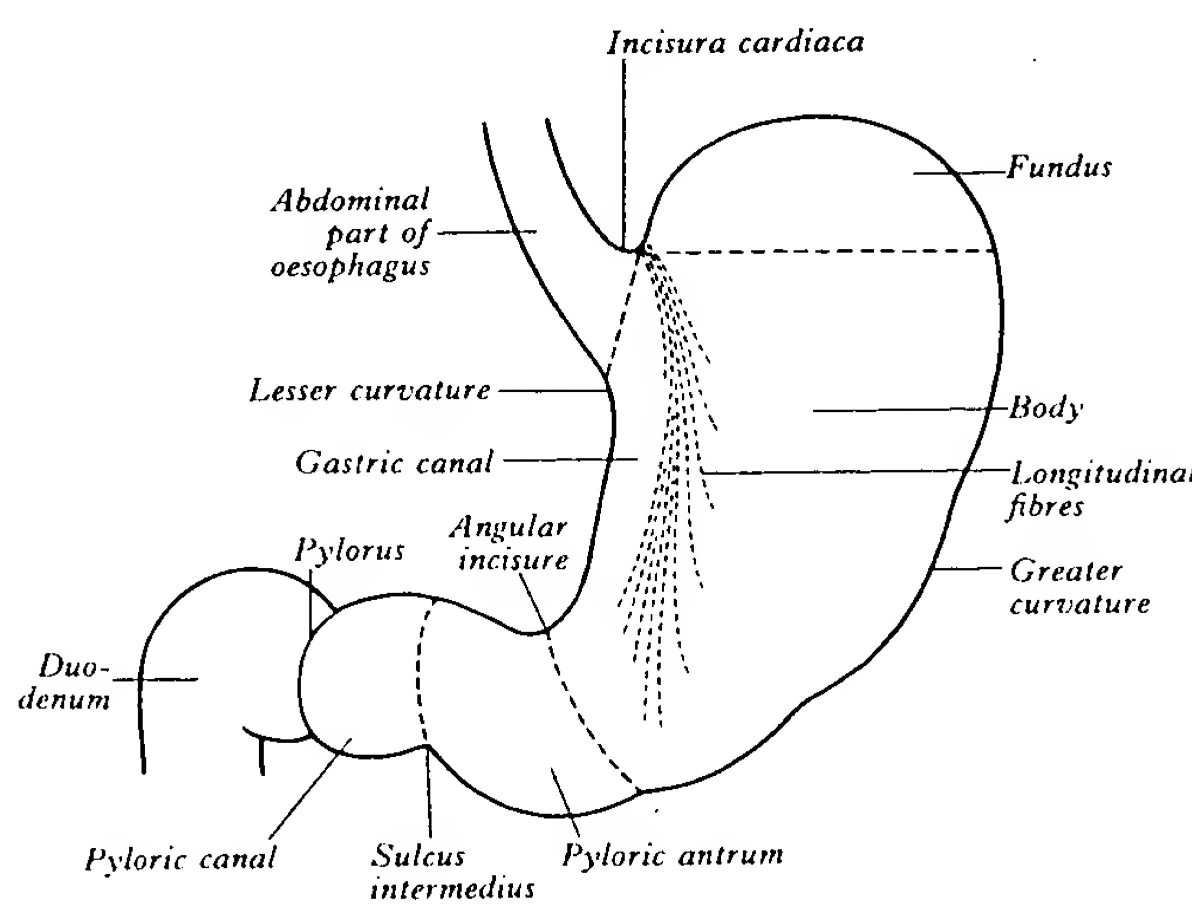
Interior of the Stomach

When examined after death, the stomach is usually fixed at some stage of the digestive process. A common form is that shown in (**8**.109). When the viscus is laid open by a section through the plane of its two curvatures, it is seen to consist of two segments: (*a*) a large globular portion on the left; and (*b*) a narrow tubular part on the right. The transition between the two regions is gradual, and this division is purely arbitrary. The cardiac incisure lies to the left of the abdominal part of the oesophagus: the projection of this notch into the cavity of the stomach increases as the organ distends, and has been supposed to act as a valve preventing regurgitation into the oesophagus. The elevation corresponding to the angular incisure is seen at the beginning, and the circular thickening of the pyloric sphincter at the end, of the pyloric region.

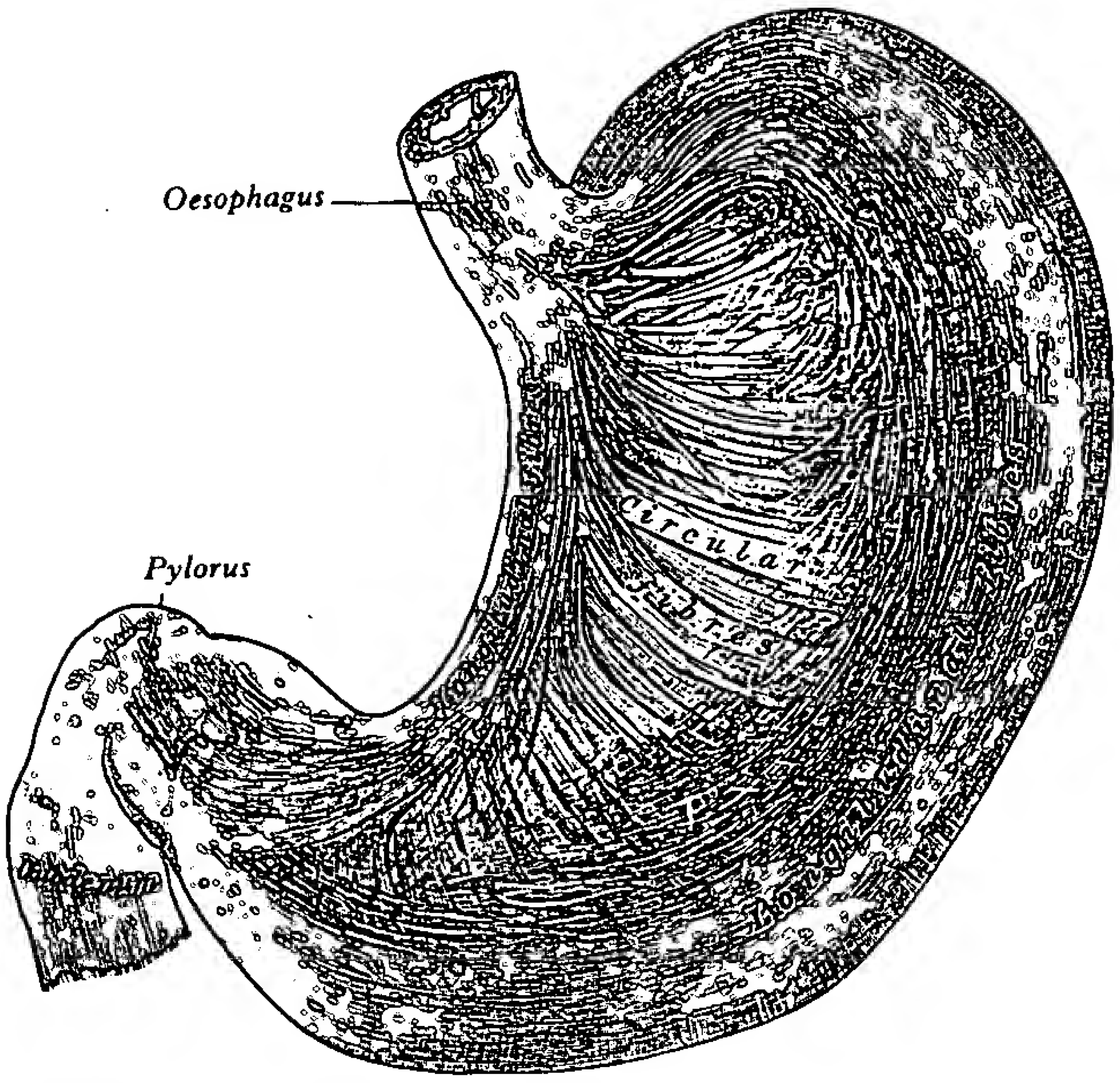
Modelling of the gastric epithelium in the human fetus (Lewis 1912) has shown that a channel (the *gastric canal*) extends along the lesser curvature from the cardiac orifice to the angular incisure (**8**.105). It was also demonstrated radiologically that such a canal exists in the adult (Jefferson 1915); in most cases examined whilst in the act of swallowing radio-opaque fluid it was found that the fluid was at first confined to the part of the stomach adjacent to the lesser curvature, and concluded that the oblique muscular coat of the stomach is so arranged that by its contraction it will cause a temporary separation of a canal along the lesser curvature.

The pyloric sphincter is a muscular ring formed by a marked thickening of the circular layer of the muscular coat. Some of the longitudinal fibres turn in and interlace with the fibres of the sphincter. (*See* DiDio and Anderson 1968.)

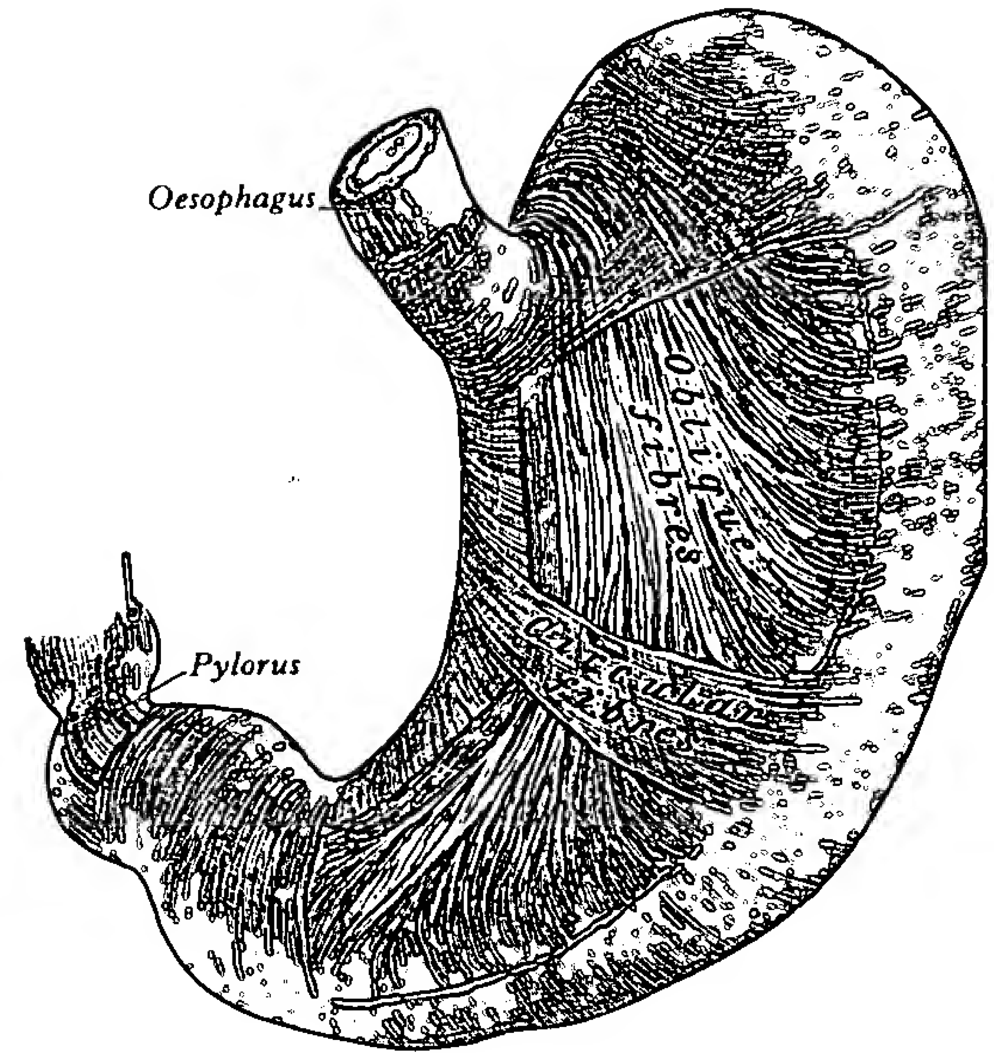
A *cardiac sphincter* is sometimes described at the oesophageal end of the stomach, formed from the circular fibres of the gastric



8.105 The parts of the stomach.



8.106 The longitudinal and circular gastric muscular fibres. Anterosuperior aspect. (Spalteholz.)



8.107 The oblique muscular fibres of the stomach, shown b
dissection of its wall. Anterosuperior aspect.

wall. Although radiological observation strongly suggests the presence of some force capable of delaying entry of oesophageal contents into the stomach, the histological evidence for this is uncertain and requires further study. It is often asserted that the muscle fibres of the right crus of the diaphragm, which decussate obliquely around the termination of the oesophagus, may exert a compressive or kinking effect at this level; but this is an anatomical speculation rather than a physiological fact. Bowden and El-Ramli (1967) have described the structure of this part of the diaphragm (see also p. 549), and they concluded that while the right crus invariably embraces the termination of the oesophagus, the relationship does not suggest an effective sphincter, although they agreed that in some positions of the trunk a kinking effect might occur. Others have suggested that the sphincter may be formed by circular muscle of the oesophageal wall (pp. 550, 1318).

GASTRIC STRUCTURE

The wall of the stomach consists of the four usual layers: serous, muscular, submucous and mucous, together with their vessels and nerves.

The serosa, or visceral peritoneum, covers the entire surface of the organ, excepting (*a*) along the greater and lesser curvatures at the lines of attachment of the greater and lesser omenta, where the two layers of peritoneum leave a small space in which vessels and nerves lie, and (*b*) a small area on the postero-inferior surface of the stomach, close to the cardiac orifice, where the stomach is in contact with the inferior surface of the diaphragm at the site of reflexion of the gastrophrenic and left gastropancreatic folds.

The muscularis externa (8.106, 107) is situated immediately beneath the serous covering, with which it is closely connected by subserous areolar tissue. It consists of three layers of visceral muscular fibres: longitudinal, circular and oblique.

The *longitudinal fibres* are the most superficial and are arranged in two sets. The first set consists of fibres continuous with the longitudinal fibres of the oesophagus; they radiate from the cardiac orifice, are best developed near the curvatures and end proximal to the pyloric portion. The second set commences in the body of the stomach and passes to the right, its fibres becoming more thickly arranged as they approach the pylorus. Some of the more superficial longitudinal fibres pass on to the duodenum, but the deeper fibres turn inwards and interlace with the fibres of the pyloric sphincter.

The *circular fibres* form a uniform layer over the whole of the stomach internal to the longitudinal fibres. At the pylorus they are most abundant, and are there aggregated into an annular mass, the *pyloric sphincter*. The circular fibres of the gastric w
continuous with those of the oesophagus, but they are :
marked off from the circular fibres of the duodenun
connective tissue septum.

The *oblique fibres*, internal to the circular layer, are
chiefly to the body of the stomach and are most developed ı
cardiac orifice. They sweep downwards from the cardia
and run more or less parallel with the lesser curvature.
right they present a free and well-defined margin (8.107)
left they blend with the circular fibres.

The peristaltic contraction of the musculature of the
antrum thoroughly mixes the stomach contents in this
returning some to the body of the stomach and propellii
into the duodenum. The pyloric sphincter contracts intern
during contraction of the antral musculature, but, w
stomach is at rest, it is relaxed, leaving the pylorus open (A
et al. 1957; Spira 1957). The exact mechanism of contr
transfer of stomach contents through the pylorus i
duodenum is still not fully clarified. For an auth
summary consult Hunt and Knox (1968).

The submucosa consists of loose, areolar tissue, cor
the mucous and muscular layers.

The mucous membrane is thick and its surface is
soft and velvety. In the fresh state it is of a pinkish tin
pyloric end, and of a red or reddish-brown colour over th
its surface. During the contracted state of the organ it is
into numerous folds or rugae which for the most par
longitudinal direction, and are best marked towards th
end of the stomach, and along the greater curvature
These folds are obliterated when the organ is distended.

STRUCTURE OF GASTRIC MUCOSA

When examined with a lens, the luminal surface of the
membrane (8.109) has a honeycomb appearance, beca
covered with small depressions or alveoli, of a polygona
like form, about 0·2 mm in diameter. These are the *gastri*
at the bottom of each are the orifices of the gastric gla
surface of the mucous membrane including the gastr
covered with a single layer of columnar secretory epithe
the *surface mucous cells*, which liberate mucus from their
to the surface of the stomach. This acts as a lubricant
protects the gastric lining against its own secretions of
enzymes. This type of epithelium commences very abrup
cardiac orifice, where there is a sudden transition
stratified epithelium of the oesophagus. The *gastr*

comprise: (1) cardiac glands; (2) main glands of the body and fundus; and (3) pyloric glands.

The cardiac glands (**8**.110A) are infrequent and confined to a small area near the cardiac orifice; some are simple tubular glands whilst others are compound racemose in type. Mucus-secreting cells predominate whilst oxyntic and zymogenic cells are infrequent.

The main gastric glands of the body and fundus, of which from three to seven open into each gastric pit, are cytologically the most highly differentiated of the gastric glands (**8**.110B, C). At least four distinct cell types have been distinguished:

(1) The *chief (peptic* or *zymogenic) cells* are present particularly in the basal parts of the glands. These are cuboidal, typical protein-synthesizing cells, containing prominent secretory bodies, much rough endoplasmic reticulum, a prominent Golgi complex, and by light microscopy they are strongly basophilic because of their contained RNA. These cells are the source of the digestive enzymes of the stomach (**8**.109).

(2) The *oxyntic (parietal) cells*, large, rounded and eosinophilic, are most numerous on the side walls and near the duct of the gland. They occur only at intervals, and with the light microscope appear to be applied to the external surface of the other cell types, or partly intercalated between their external aspects. They bulge into the adjacent lamina propria, producing a moniliform or beaded appearance. They are connected with the lumen of the gland by fine processes that pass between the adjacent cells. Ultrastructural studies have shown that the oxyntic cells possess tortuous intracellular canaliculi, the surfaces of which are covered with microvilli, and which open directly into the lumen of the gland on the apices of the fine processes which pass centrally between the adjacent cells as mentioned above. Each cell possesses a large, round, centrally-placed nucleus, and the surrounding cytoplasm carries only sparse endoplasmic reticulum and no secretory granules, but a very large number of closely packed mitochondria. Minute smooth-walled membranous tubules converge on, and open into, the intracellular canaliculi (**8**.109).

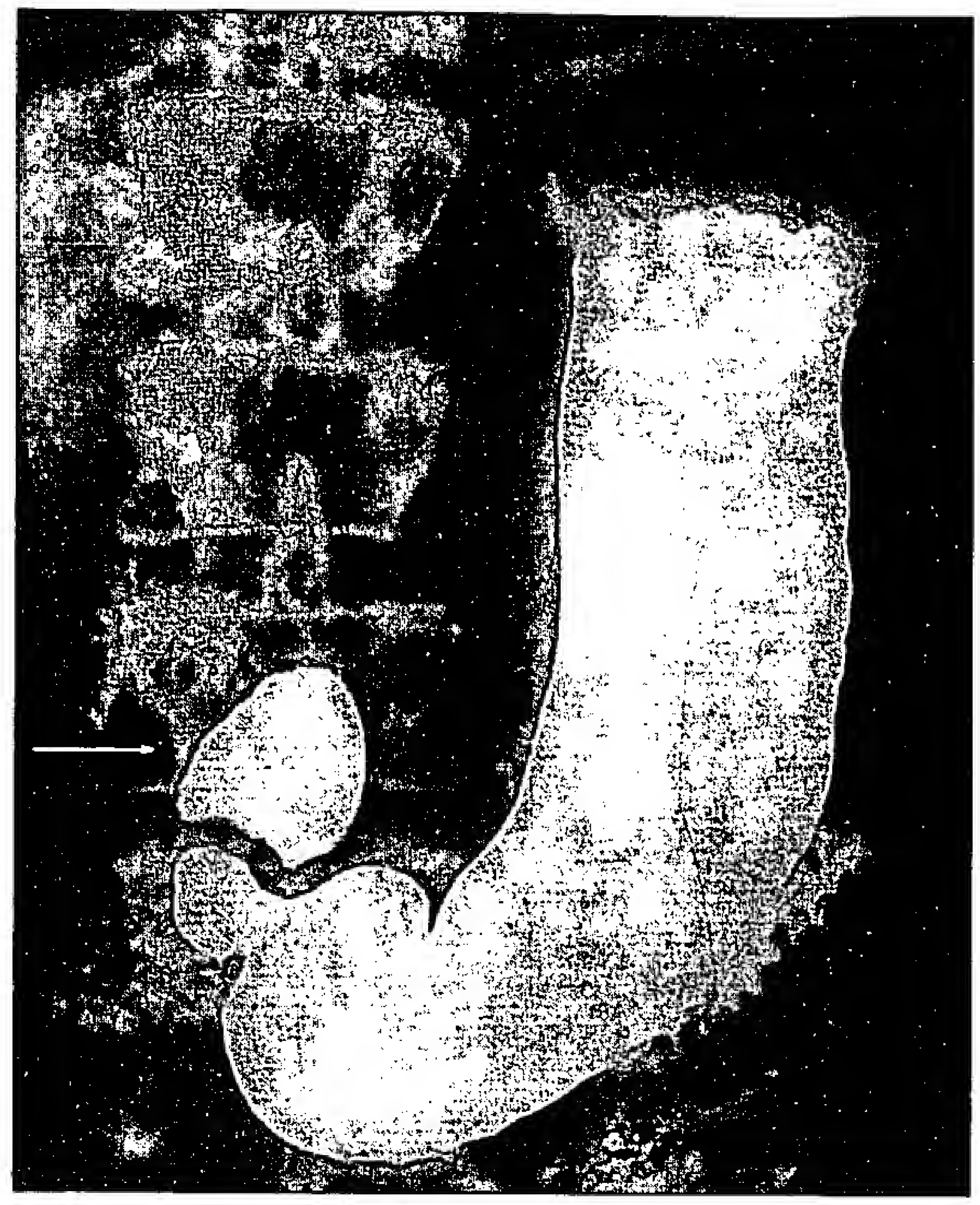
(3) *Mucous 'neck' cells* are disseminated between the other types of cell and are particularly numerous around the necks of the glands. They are typical mucus-secreting cells, but their secretions are distinct histochemically from those of the surface mucous cells.

(4) *Argentaffin cells* occur in all types of gastric gland but more commonly in those of the body and fundus than in the pyloric glands. They are more usual in the deeper parts of the gland, lying between the zymogenic cells and the basal lamina; they rarely reach the glandular lumen. Their irregular nuclei are surrounded by a granular cytoplasm which is impregnated strongly with silver-staining methods. Ultrastructurally, the cytoplasm contains many dense membrane-bound vacuoles of varying size, some of which are large (0·3 μm diameter) and which are responsible for the staining reaction. These cells are part of the gastroenteropancreatic endocrine system, described in detail elsewhere (p. 1364), and are now subdivided into a variety of types on the basis of differences in their detailed ultrastructure and secretions (**8**.109, 129).

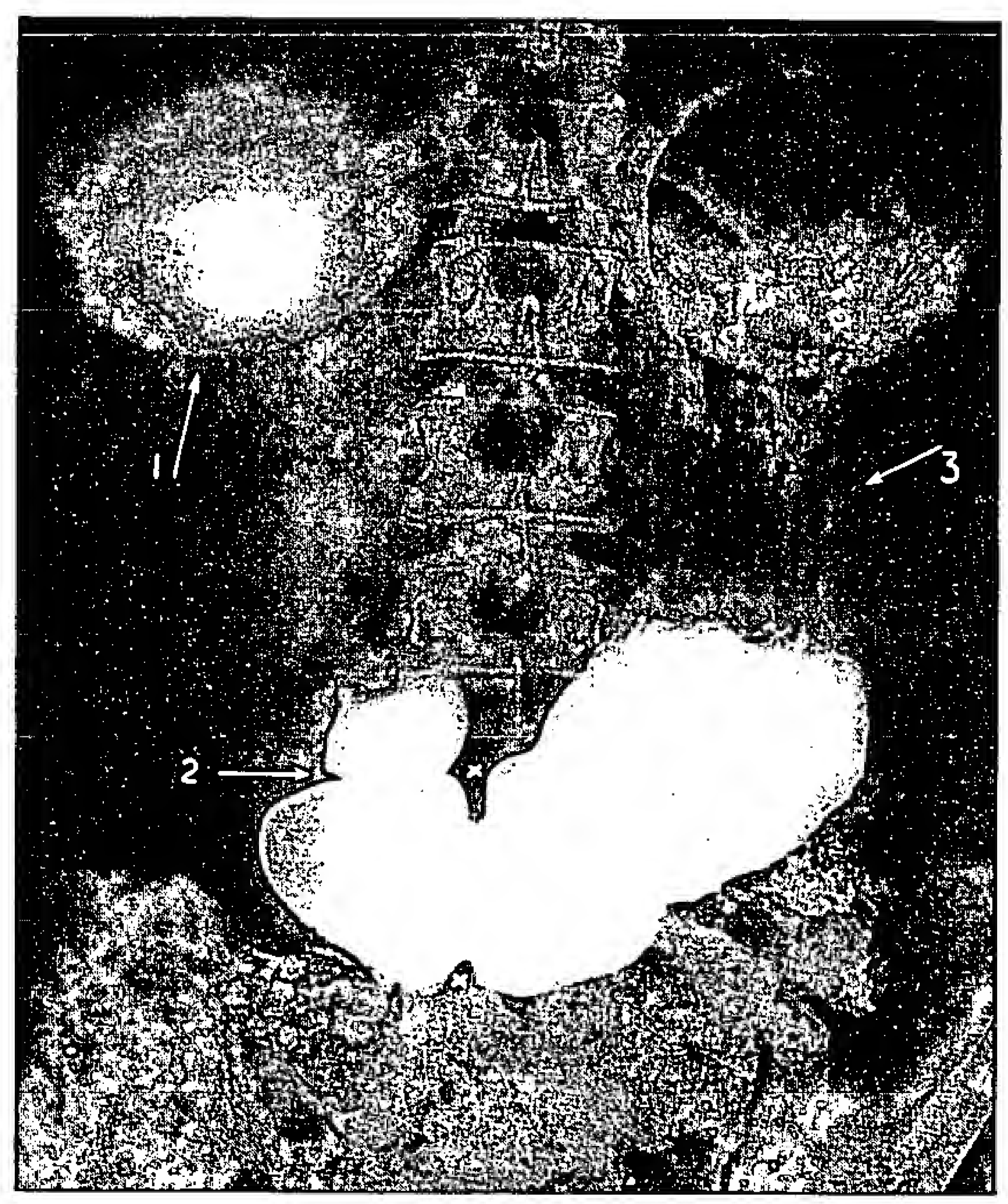
(5) *Undifferentiated columnar cells* are also present in smaller numbers, and these appear to be the origin of new cells to replace the existing ones as they are lost. Surface mucous cells last for about three days, and mucous neck cells for about one week. Other cell types appear to live considerably longer.

The pyloric glands each consist of two or three short convoluted tubes opening into a conical pit, which occupies about two-thirds of the depth of the mucous membrane (**8**.110D). The epithelial cells are predominantly mucous in type, oxyntic cells being sparse. The enteric hormone *gastrin* has been isolated from these glands in man. Gastrin is released by mechanical stimuli, and acts to increase stomach motility and the secretory activity of chief and oxyntic cells (see also p. 1365).

Although the oxyntic cells are relatively few in pyloric glands, they are apparently invariably present, both in fetal and postnatal material; in adults they may also appear in the mucous membrane of the duodenum, but only in its proximal part, near the pylorus (Leela and Kanagasuntheram 1968).

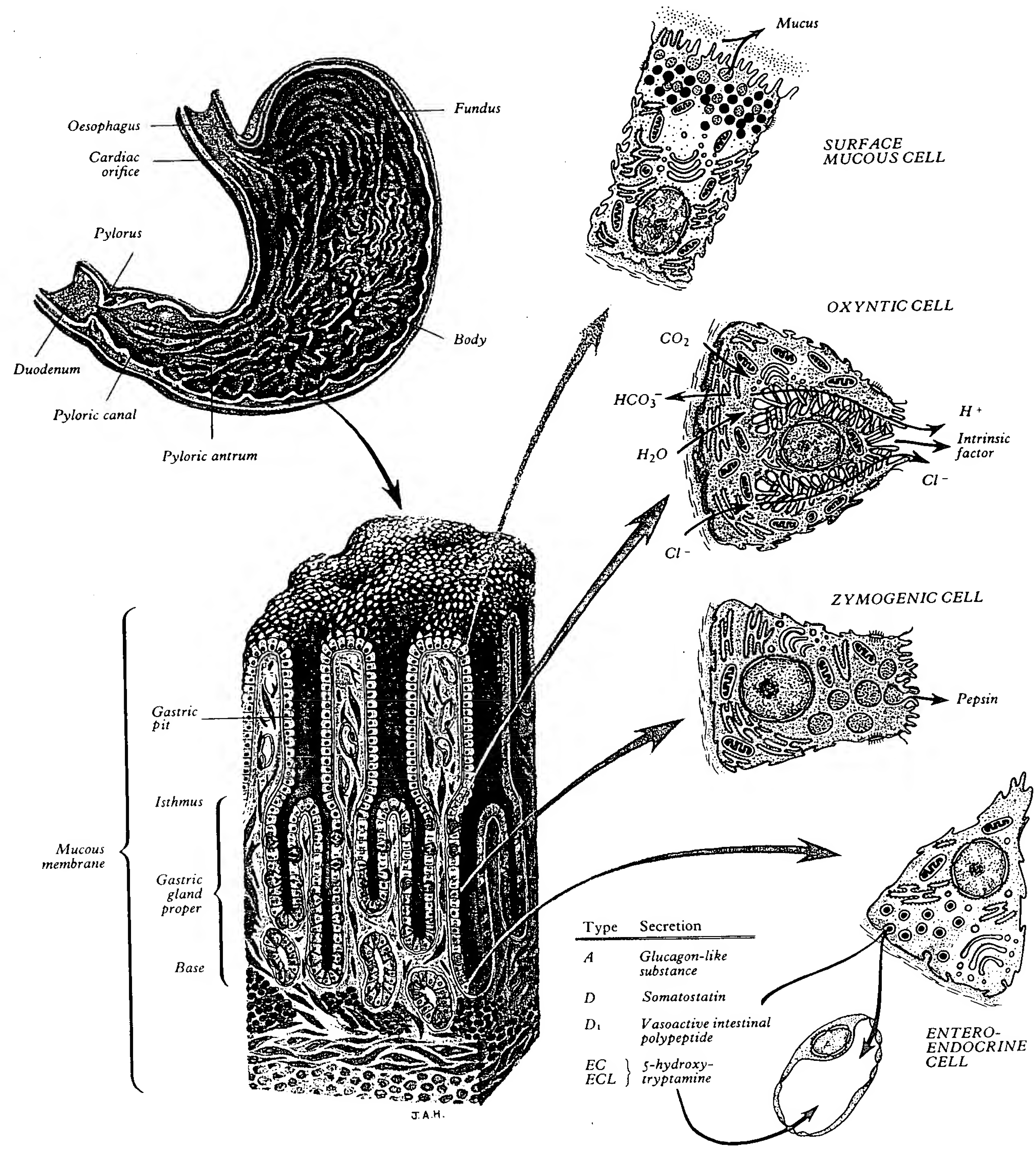


8.108A Radiograph of a normal stomach after a barium meal. The tone of the muscular wall is good and supports the weight of the column in the body of the organ. The arrow points to the duodenal cap, below which a gap in the barium indicates the position of the pylorus.



8.108B Radiograph of an atonic stomach after a barium meal. Note that this stomach contains the same amount of barium suspension as the stomach in **8**.108A. Arrow 1 points to the shadow of the right breast, arrow 2, to the pylorus, arrow 3, to the upper part of the body of the stomach, where longitudinal folds can be seen in the mucous membrane. XX marks a wave of peristalsis.

Between the glands the lamina propria consists of a connective tissue framework, and lymphoid tissue. In places, this latter tissue, especially in early life, is collected into little masses which resemble the solitary follicles of the intestine, and are termed the *gastric lymphatic follicles*. In the mucous membrane, deep to the glands, is a thin stratum of nonstriated muscle fibres, the *muscularis mucosae*; it consists of an inner circular and an outer



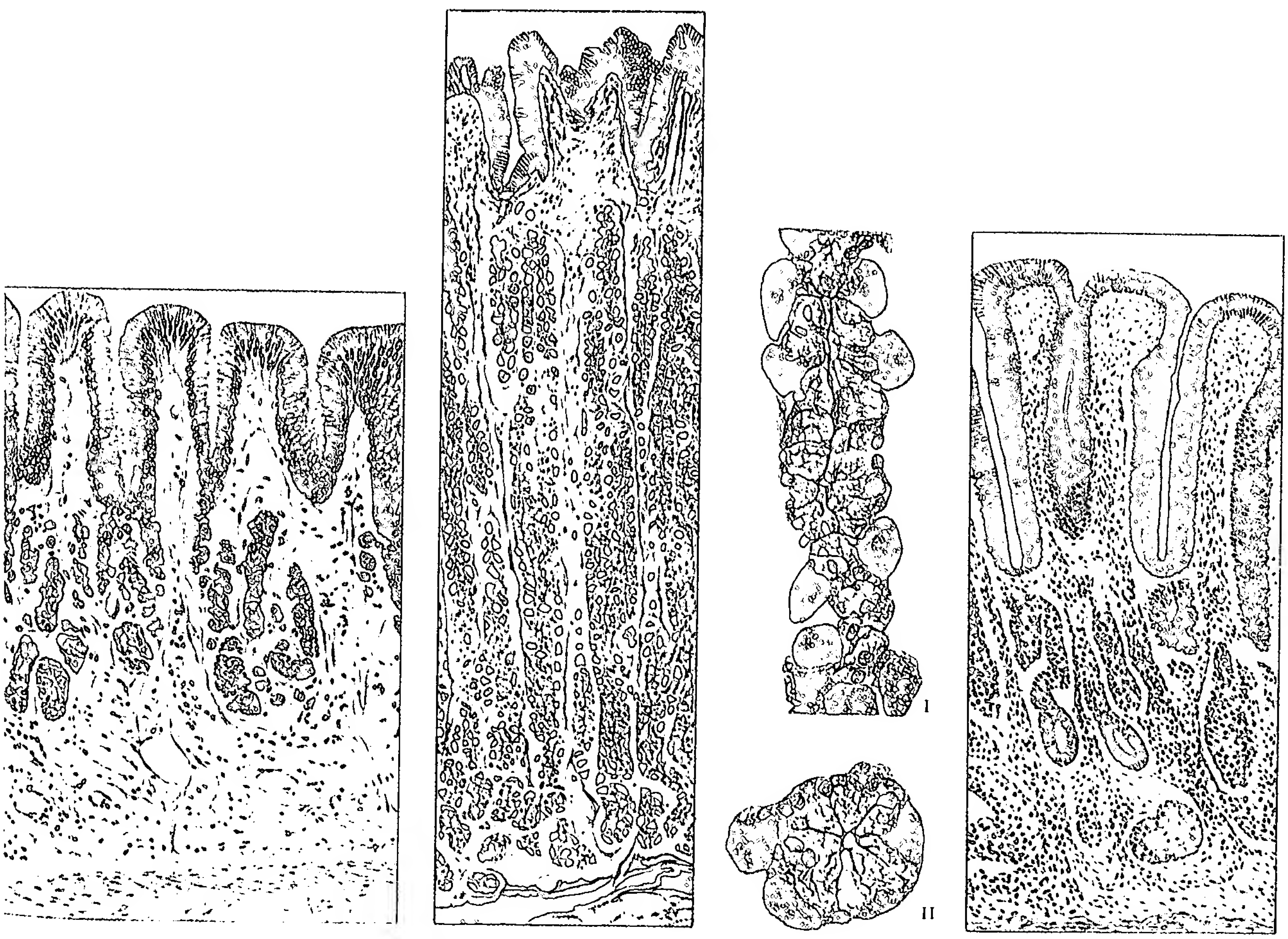
8.109 A diagram showing the principal regions of the interior of the stomach, and the histology and ultrastructure of its mucous membrane. Undifferentiated, dividing, cells are shown in white.

longitudinal layer (with a third, outer circular layer, in places). The inner layer sends strands between the glands, the contraction of which probably aids the emptying of the glands.

Vessels and Nerves

The stomach is supplied by the left gastric artery (from the coeliac artery), the right gastric and right gastro-epiploic arteries (from the common hepatic artery), and the left gastro-epiploic and short gastric arteries (from the splenic artery). These vessels not only anastomose extensively on the serosal surface of the stomach, as described elsewhere (p. 712), but they also form anastomotic networks in their intramural distribution at intramuscul: submucosal, and mucosal levels; but it is at the submucosal le that a true plexus of small arteries and arterioles is deployed. Tl *submucosal plexus*, from which the mucosa is supplied, prese considerable regional variations, not only in the gastric wall, t also in the proximal part of the duodenum. In view of the possil implications of a vascular factor in the genesis of peptic ulcer these regions, the local details of angio-architecture are considerable interest. It has been claimed that arteriovenc anastomoses occur in the gastroduodenal mucosa (Spanner 19: De Busscher 1948; Barlow *et al.* 1951; Boulter and Parkes 196

and that dysfunction in these might produce local ischaemia and hence ulceration. Mucosal end-arteries have also been described, and larger vessels such as the supraduodenal artery (p. 713) have similarly been designed end-arterial. These problems have been most recently discussed, from the anatomical point of view, by Piasecki (1974, 1977), and the results of his observations on fetal, neonatal, and adult human stomachs, injected with India ink, form the basis of this account of the gastric intramural arteries. From the anastomotic arcades formed along the greater and lesser :urvatures by the main arteries of supply mentioned above, large numbers of branches pass on to both anterior and posterior ıspects of the stomach, in directions approximately transverse to :he organ's long axis. In addition to these *anterior* and *posterior ;astric arteries* smaller rami, which are often paired, pass directly :owards the part of the gastric wall subjacent to attachments of ›menta. As these vessels ramify on the external surface and then ɔenetrate the muscular layer of the wall to reach the submucous ınd mucosal levels of connective tissue, they form plexuses— ;ubserosal, intramuscular, and submucosal, of which the second s the most richly developed (8.111B, C). The muscular plexus is ;upplied by branches from both the subserous and submucosal ɔlexuses, and the muscular vessels vary in direction in the lifferent laminae of muscle, perhaps in adaptation to their :haracteristic directions of contraction. The arteries of the ;ubmucosa anastomose freely, but the incidence of arterial ınastomoses varies in different regions. Counts by Piasecki (1974) ;howed that while the *number* of anastomoses along, for example, the lesser curvature increased from its cardiac to its pyloric end, the mean calibre of the anastomosing arteries showed a reverse tendency. The mucosal arteries, which fill the capillary networks supporting the epithelium and its glands, are chiefly derived from the submucous plexus; but along both curvatures a few mucosal arteries are derived directly from extramural (subserosal) sources. These pass through the muscular layers and submucosa, often without lateral communications with submucosal arteries. The incidence of these vessels apparently increases from the cardiac to the pyloric region of the stomach in man. The capillary networks supplied by them are largely independent of those fed by adjacent submucosal arteries, and to that extent the patch of mucosa supplied by such a vessel may be considered more vulnerable to vascular obstruction. According to Piasecki mucosal arteries in general do not form lateral anastomoses, but since their submucosal feeders do, vascular obstruction is to that degree less likely. The same observer examined the pyloric canal and sphincter, and showed a different pattern of supply. Rami of the right gastric and gastro-epiploic arteries (*'pyloric' arteries*) pierce the duodenum immediately distal to the pyloric sphincter around its entire circumference, passing through the muscular layer to reach the submucosa, where each divides into two or three branches. These turn into the pyloric canal, internal to the sphincter, to traverse the submucosa as far as the termination of the pyloric antrum (8.111C), supplying the whole of the mucosa of the pyloric canal. Branches of these pyloric submucosal arteries may anastomose at their commencement with duodenal sub-



B C D

110A Vertical section through the mucous membrane of the cardiac ırt of the stomach (human). Stained with haematoxylin and eosin. lagnification about × 150.

110B Vertical section through the mucous membrane of the fundus of ıe stomach (cat). Stained with haematoxylin and eosin. Magnification ›out × 100. Note the beaded appearance given by the oxyntic cells.

8.110C (I) Gland from fundus of stomach (cat). (II) Lower part of gland cut transversely. Stained with haematoxylin and eosin. Magnification about × 530. The peripherally placed cells staining deeply with eosin are the oxyntic cells.

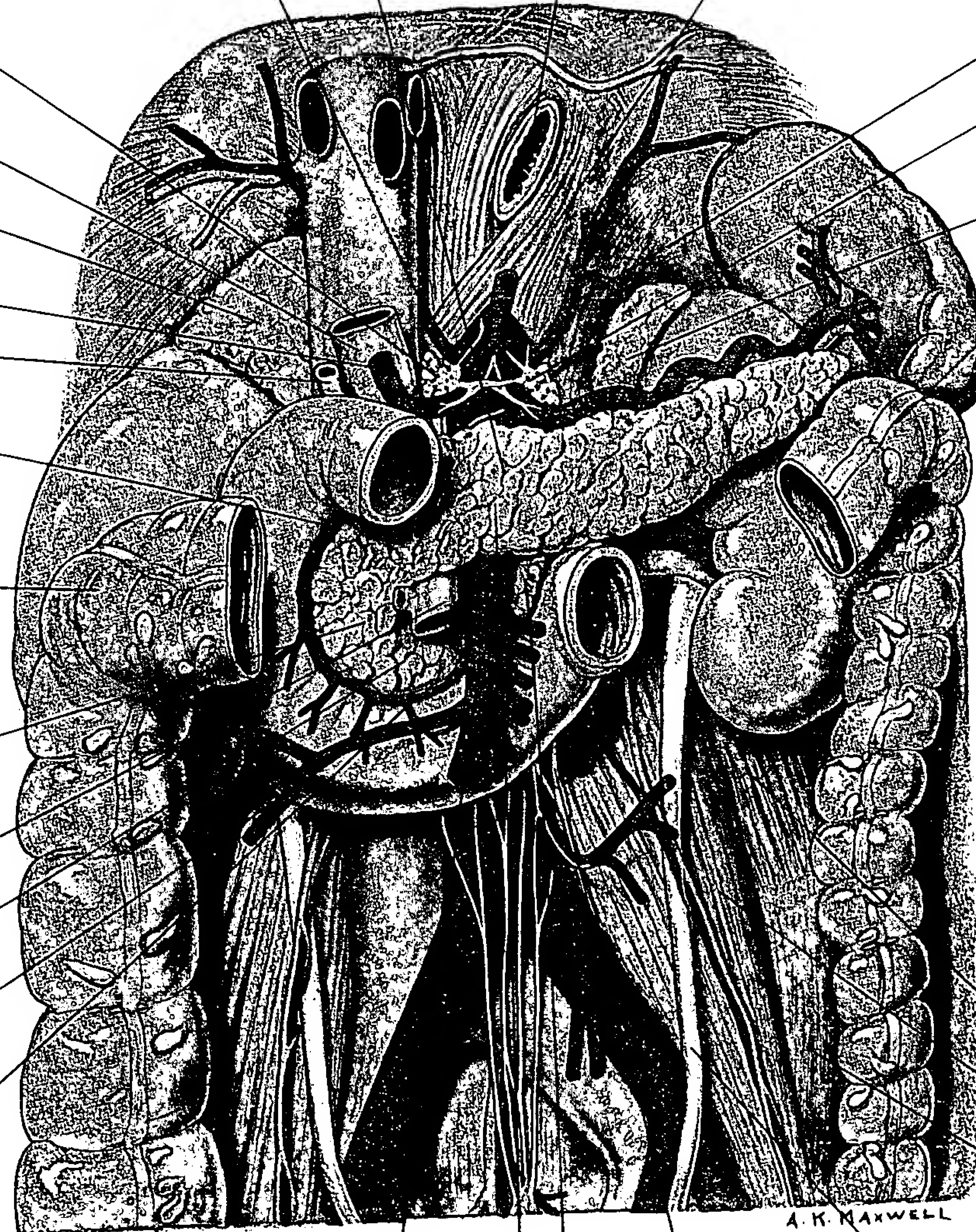
8.110D Vertical section through the mucous membrane of the pyloric part of the stomach (cat). Stained with haematoxylin and eosin. Magnification about × 75.

mucosal arteries and, by their terminal branches, with the corresponding gastric arteries. The pyloric sphincter itself is supplied by gastric and pyloric arteries, rami of both of which leave their parent vessels in the subserosal and submucosal parts of their courses to penetrate the sphincter.

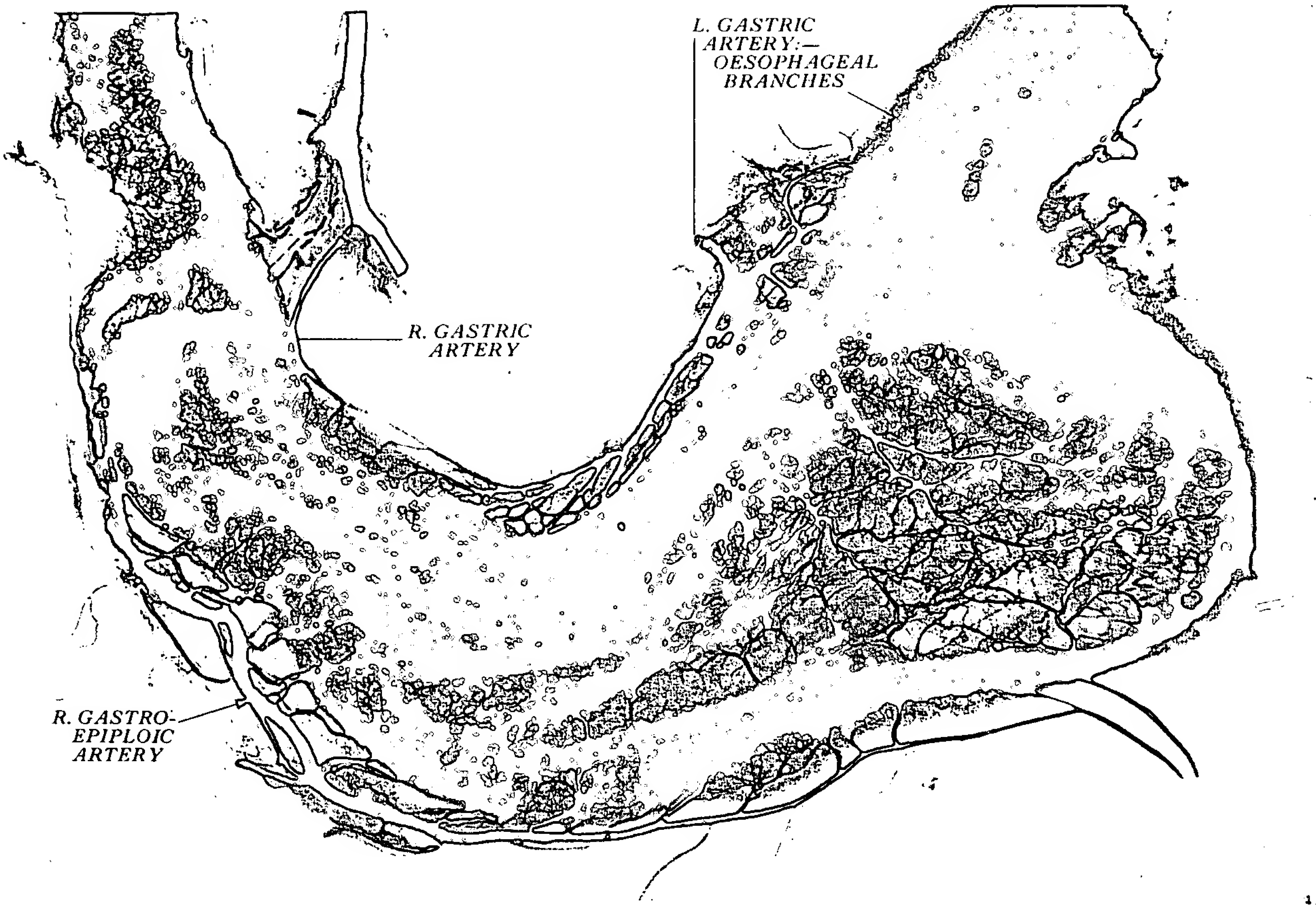
The gastric veins commence as straight vessels between the glands of the mucosa, and these drain into submucosal veins. Their further arrangement has not received the same attention as the corresponding arteries; but the larger veins accompany the main arteries to their ultimate drainage into the splenic and superior mesenteric veins, while some pass directly to the portal vein. The smaller lymphatic vessels are said to resemble the veins in distribution. The regional lymph nodes and their final drainage are described on p. 793.

The *nerves* are derived from multiple sources. The sympathetic supply is mainly from the coeliac plexus through the plexuses around the gastric and gastro-epiploic arteries. Some branches from the plexus around the hepatic artery proper reach the lesser curvature by passing between the layers of the hepatogastric ligament (p. 1327). Branches from the left phrenic plexus pass to the cardiac end of the stomach, which also receives a twig from the branch of the left phrenic nerve to the right crus of the diaphragm. Inconstant branches are given to the stomach from the left thoracic splanchnic nerves and from the thoracic and lumbar sympathetic trunks.

The parasympathetic supply is derived from the vagus nerves. Usually one or two nerve trunks lie on the anterior and one or two on the posterior aspect of the gastro-oesophageal junction; the anterior nerves comprise for the most part left vagal fibres, and the posterior right vagal fibres, which have emerged from the oesophageal plexus. The anterior nerves supply several filaments to the cardiac orifice and then divide near the upper end of the lesser curvature into branches. Of these: (*a*) *gastric branches* (4–10) radiate on the anterior surface of the body and fundus of the stomach; one is larger than the others and lies in the lesser omentum near the lesser curvature (the *greater anterior gastric nerve*); (*b*) *pyloric branches*, generally two in number, one running almost horizontally to the right in the lesser omentum towards its free edge and then turning down on the left side of the hepatic artery proper to reach the pylorus, the other usually arising from



8.111A A dissection to show the duodenum, pancreas, stem arterial rami of the gastro-intestinal tract, and surrounding structures. The right and left hepatic veins have been cut away at their points of entry into the inferior vena cava. The superior hypogastric plexus is shown in front of the sacral promontory and the sympathetic nerves which form it are seen descending across the bifurcation of the aorta, the left common iliac vein and the body of the fifth lumbar vertebra. (In this specimen the left renal artery is situated anterior to the left renal vein at the hilum of the kidney.)



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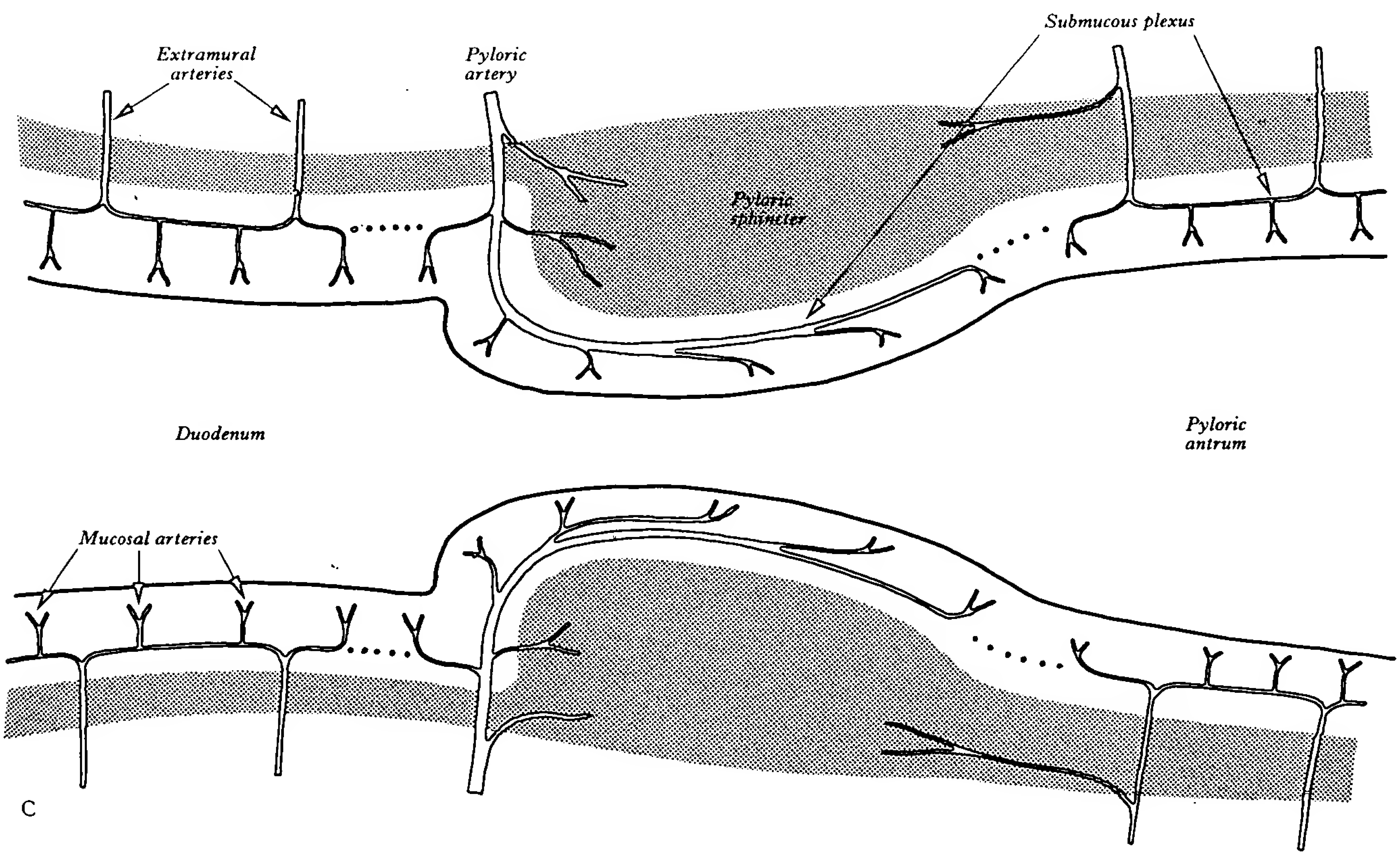


C

8.111B and C Blood supply of the stomach and the proximal duodenum. B Arterial system in a fetal human stomach. The muscle layer has been removed. Note double arcade along the lesser curvature. The arteries have been injected with a mixture of 2 per cent gelatin and Indian ink and subsequently cleared by the Spalteholz technique. (Magnification approximately ×6.) C A scheme of arterial arrangements at the gastroduodenal junction. Dotted lines indicate sites where the submucous plexus may be deficient in continuity. Shaded areas represent the muscular layer of the visceral wall. (By courtesy of Dr. C. Piasecki, Department of Anatomy, Royal Free Hospital School of Medicine, London, and the *Journal of Anatomy*.)

the greater anterior gastric nerve and passing obliquely to the pyloric antrum. The posterior nerves give off two main sets of branches: (*a*) *gastric branches*, radiating on the posterior surface of the body and fundus of the stomach; they extend on to the pyloric antrum but do not reach the pyloric sphincter; one of these is larger than the rest and passes along the posterior margin of the lesser curvature (*greater posterior gastric nerve*), giving branches to the coeliac plexus; (*b*) *coeliac branches*, which are larger than the gastric branches, and pass in the lesser omentum to the coeliac plexus. No true plexiform array of nerves occurs on either the anterior or posterior surface of the stomach. Nerve plexuses are found in the submucosal coat and between the layers of the muscular coat. The latter corresponds to the myenteric (*Auerbach's*) plexus of the intestine and contains numerous nerve cells. From these plexuses fibres are distributed to the muscular tissue and the mucous membrane.

The vagus has both secretory and motor influences on the stomach; stimulation evokes a secretion rich in pepsin and increased gastric motility, while after vagotomy the stomach becomes flaccid and empties slowly. The sympathetic supplies vasomotor fibres to the gastric blood vessels and provides the main pathway for pain fibres from the stomach.

The Small Intestine

The small intestine is a convoluted tube, extending from the pylorus to the ileocaecal valve, where it joins the large intestine. It is often stated to be 6 to 7 m long, and gradually diminishes in diameter from its commencement to its termination. However, the small intestine is longer after death owing to the absence of muscle tone; during life its average length in the adult is said to be about 5 m (*see* below). It has been reported (Underhill 1955) that in 109 adult subjects shortly after death the small intestine ranged in length from 3·35 to 7·16 m in women and from 4·88 to 7·85 m in men, the average length being 5·92 m in women and 6·37 m in men. The length was found to be correlated with the height of the individual, but independent of the age. The large intestine was found to be much more constant in length in this particular study. Jit and Grewal (1975) have reviewed the literature on this topic, reporting their own findings in a series of 137 Indian subjects. They confirmed an association with height, and the lack of it with weight. They observed a variable reduction in length after fixation in formalin, a contraction which sometimes reached 44 per cent. Various observers have passed flexible tubes through the alimentary canal, recording total lengths of from 2·7 m to 4·5 m (cited by Jit and Grewal 1975).

The small intestine lies in the central and lower parts of the abdominal cavity and usually within the confines of the large intestine; it is in relation, in front, with the greater omentum and abdominal wall; a portion of it extends down into the pelvis and lies in front of the rectum. The small intestine consists of: (1) a short, curved section which is devoid of a mesentery and is named the *duodenum*; and (2) a long, greatly coiled part which is attached to the posterior abdominal wall by the mesentery (p. 1329), and of which the proximal two-fifths constitutes the *jejunum*, and the distal three-fifths the *ileum*.

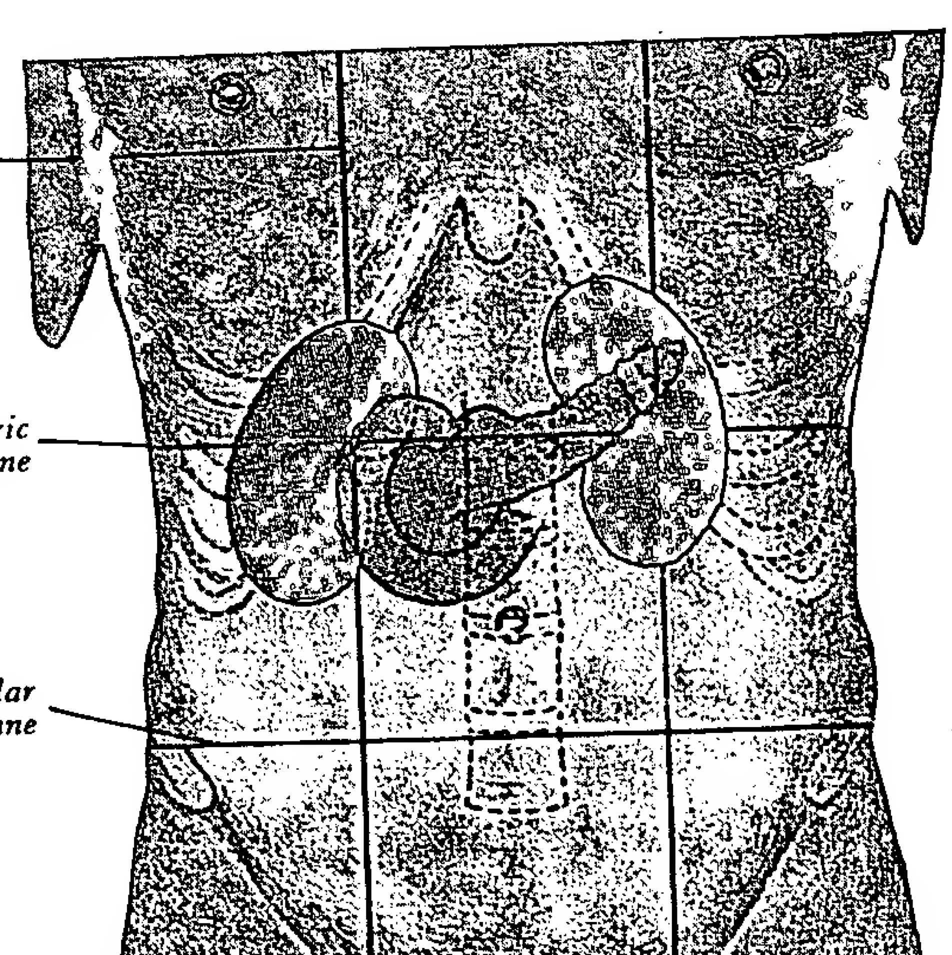
THE DUODENUM

The duodenum (**8**.111A), 20–25 cm long, is the shortest, widest and most fixed part of the small intestine; it has no mesentery, and thus is only partially covered with peritoneum. Its course presents a remarkably constant curve, somewhat of the shape of an incomplete circle, which encloses the head of the pancreas. It lies entirely above the level of the umbilicus.

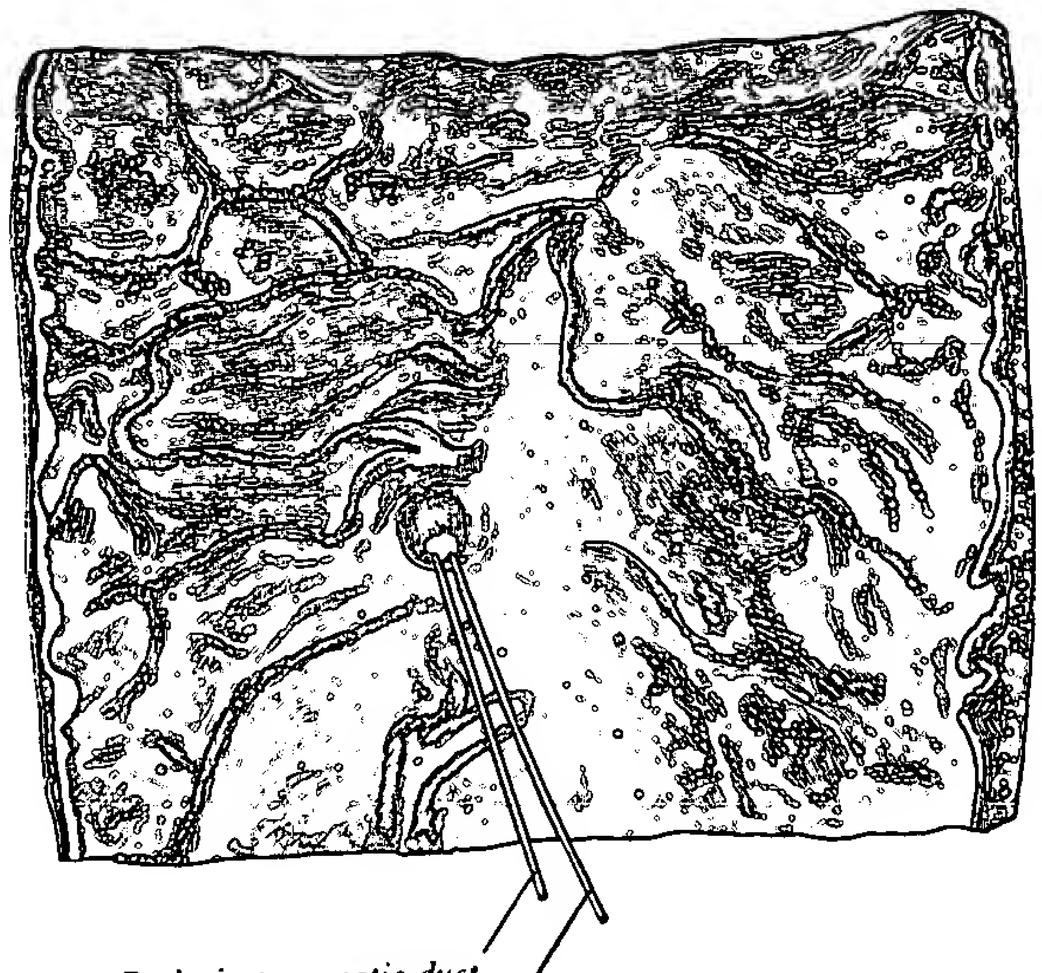
It begins at the pylorus, passes backwards, up and to the right for about 5 cm, under cover of the posterior part of the quadrate lobe of the liver, to the neck of the gall bladder, varying slightly in direction according to the degree of distension of the stomach; it then makes a sharp curve (*superior duodenal flexure*) and descends for about 7·5 cm in front of the medial part of the right kidney, usually to the level of the lower border of the body of the third lumbar vertebra, just medial to the lateral plane (**8**.112). Here it makes a second bend (*inferior duodenal flexure*), and passes horizontally to the left across the vertebral column for about 5–10 cm, just above the level of the umbilicus, having a slight inclination upwards; it then ascends in front and to the left of the abdominal aorta for about 2·5 cm, and ends opposite the second lumbar vertebra in the jejunum. At its union with the jejunum it turns abruptly forwards, forming the *duodenojejunal flexure*, which is situated 2·5 cm to the left of the median plane and 1 cm below the transpyloric plane. For descriptive purposes it is divided into first, second, third and fourth parts. The first and second parts are respectively superior and descending, while the third and fourth parts are described as horizontal and ascending.

DUODENAL RELATIONS

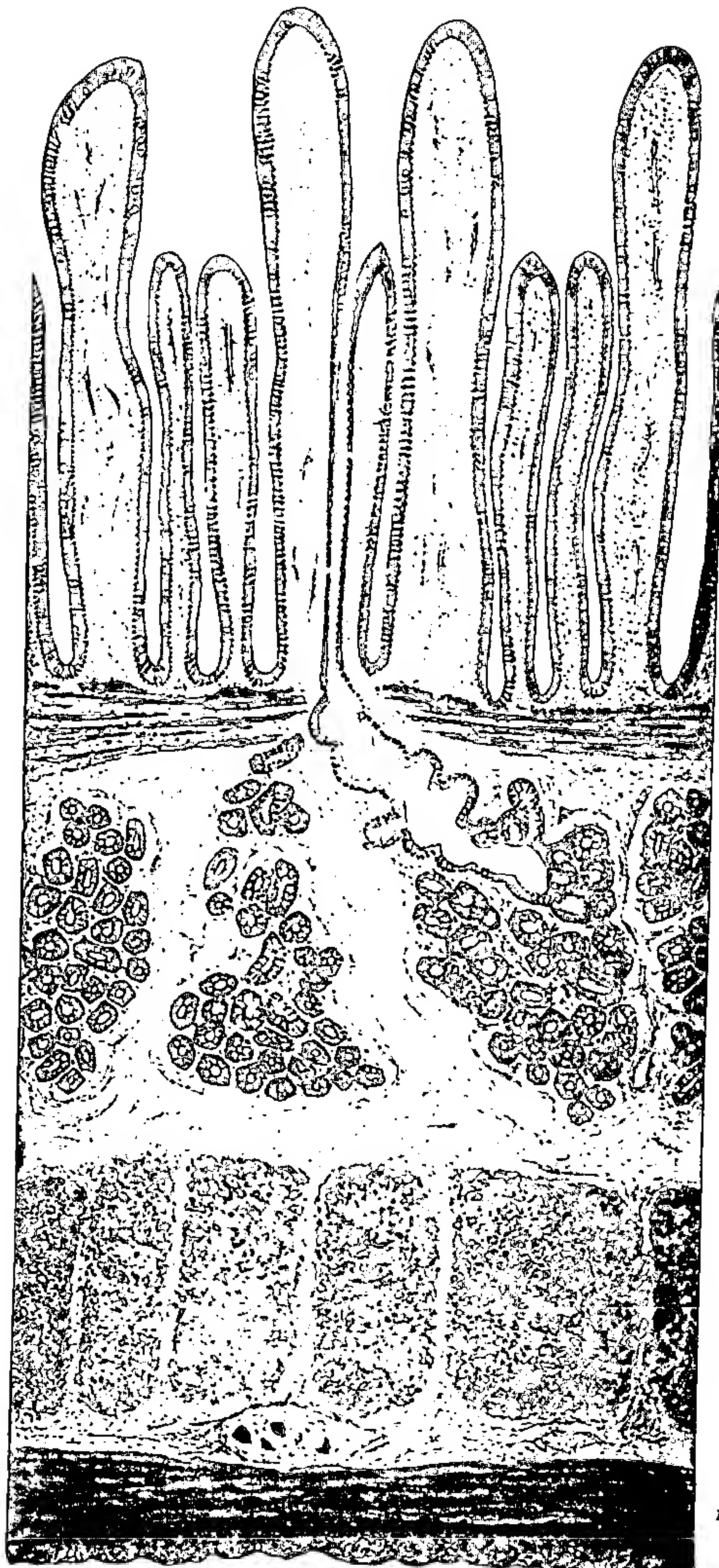
The superior part (*first part*) is about 5 cm long, and is the most movable of the four sections; it begins at the pylorus, and ends at the neck of the gall bladder. It is covered with peritoneum over the whole of its anterior aspect, but it is devoid of peritoneum posteriorly, *except near the pylorus*, where it takes a small part in the formation of the anterior wall of the omental bursa; the right part of the lesser omentum is attached to the upper border, and



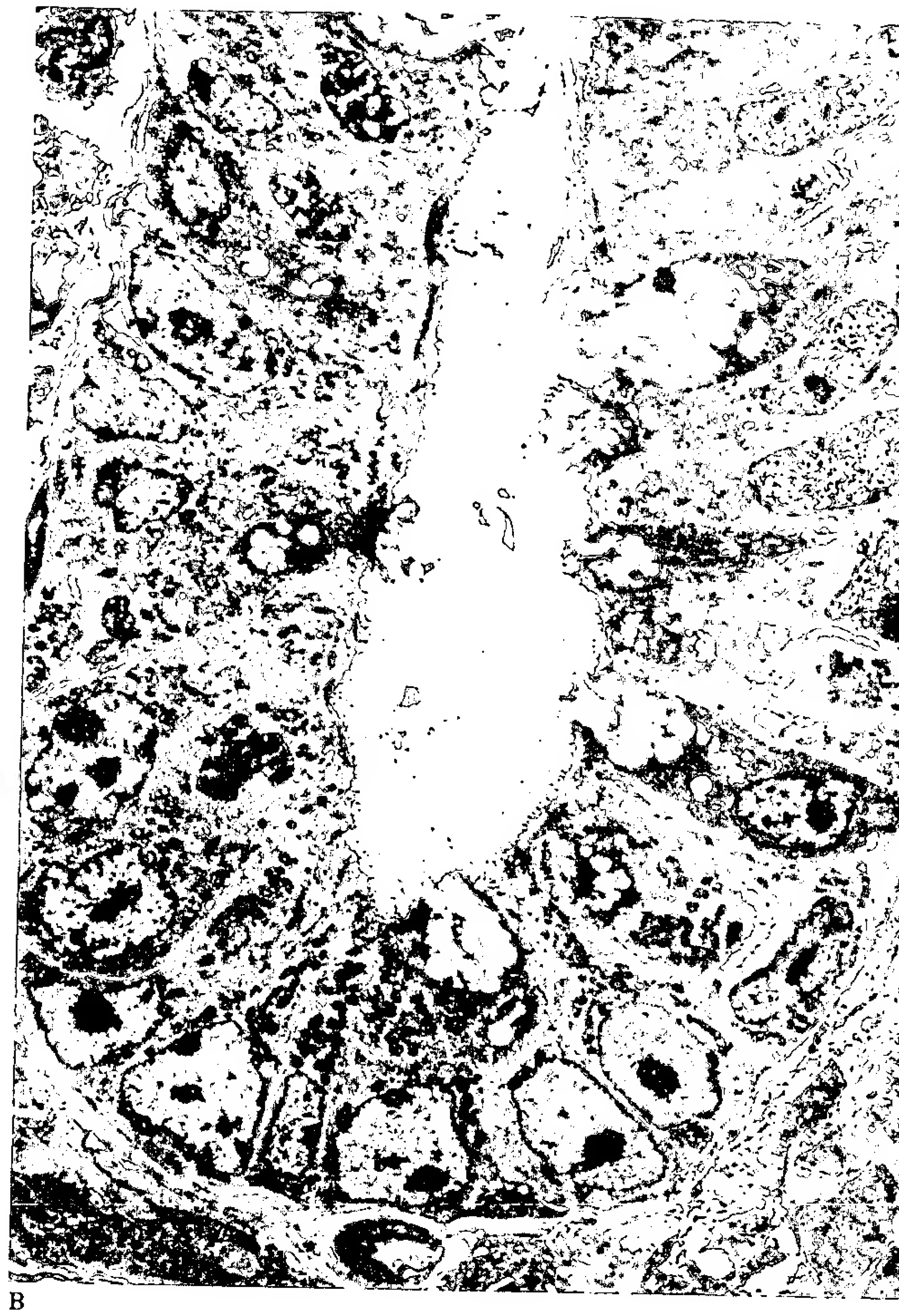
8.112 The surface projection of the duodenum, pancreas and kidneys. The vertebra just above the umbilicus is the 3rd lumbar.



8.113 The interior of the descending (second) part of the duodenum showing the major duodenal papilla.



A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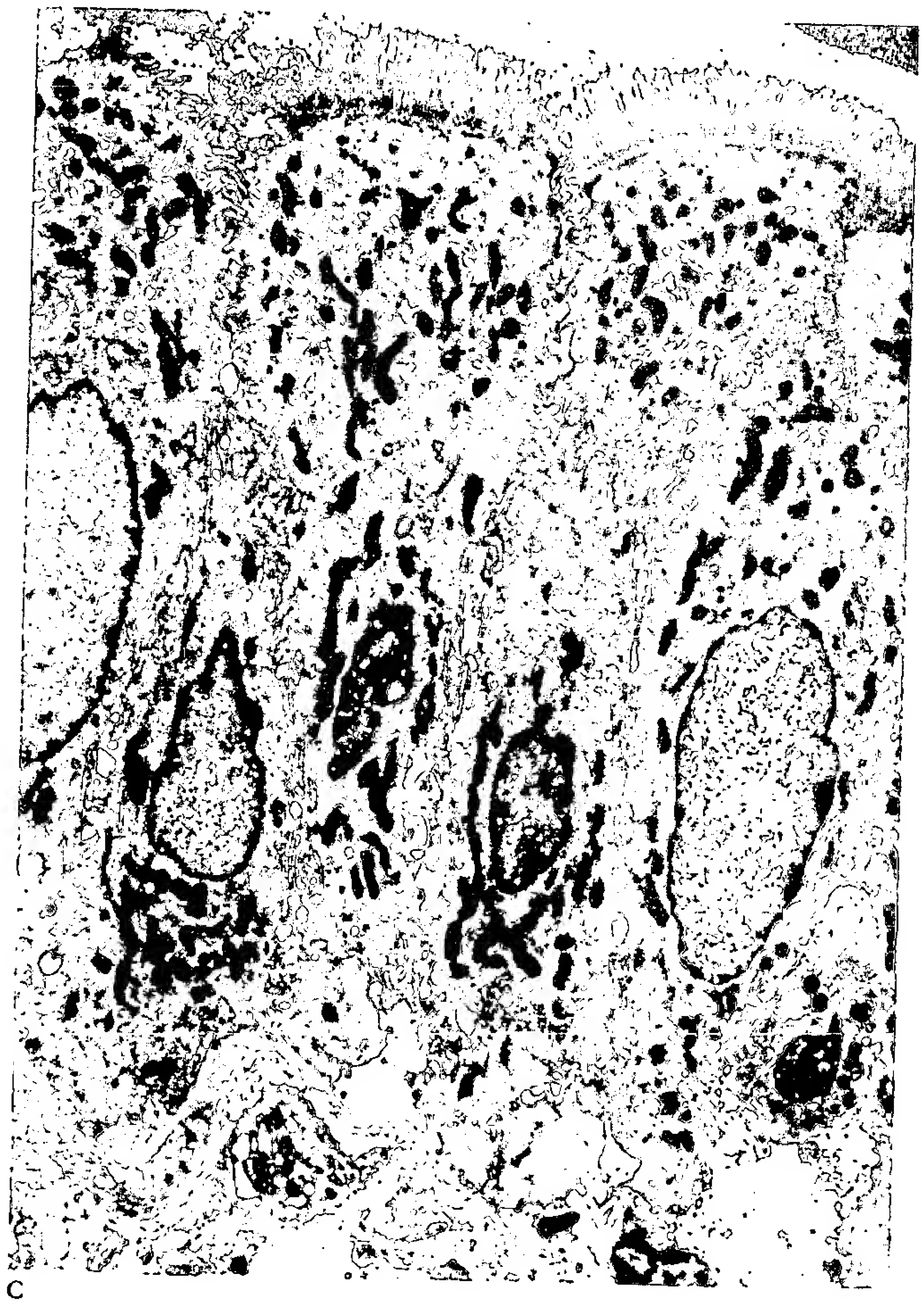

C

8.114A–C A A longitudinal section of feline duodenal wall. (Magnification about ×60.) B Electron micrograph of the base of a duodenal crypt showing absorptive columnar epithelial cells interspersed with mucus-secreting goblet cells (rat). (Magnification ×1,700.) C Electron micrograph showing absorptive columnar epithelial cells of a duodenal villus (rat). (Magnification ×3,700.) (Specimens B and C prepared and photographed by Mrs. Susan Smith, Department of Anatomy, Guy's Hospital Medical School, London.)

the greater omentum to the lower border of the proximal half. It is in relation above and in front with the quadrate lobe of the liver and the gall bladder; above, and on a more posterior plane, with the epiploic foramen; behind, with the gastroduodenal artery, the bile duct and the portal vein, and below and behind, with the head and neck of the pancreas. It is in such close relation with the gall bladder that it is usually found to be stained by bile after death, especially on its anterior surface.

The descending part (*second part*), from 8 to 10 cm long, descends from the neck of the gall bladder along the right side of the vertebral column as low as the lower border of the body of the third lumbar vertebra. It is crossed by the transverse colon, the posterior surface of which is connected to the duodenum by a small quantity of areolar tissue. The parts above and below the transverse colon are covered in front with peritoneum. It is in relation, in front, from above downwards, with the duodenal impression on the right lobe of the liver, the transverse colon and the root of the transverse mesocolon, and the jejunum; behind, it has a variable relation to the front of the right kidney in the neighbourhood of its hilum, and is connected to it by loose areolar tissue; the right renal vessels, edge of the inferior vena cava, and psoas major are also behind it. Its medial side is related to the head of the pancreas and the bile duct; its lateral side, to the right colic

flexure. Sometimes a small part of the head of the pancreas is actually embedded in the wall of the descending part of the duodenum. The bile duct and the pancreatic duct come into contact at the medial side of this part of the duodenum. The two ducts enter the wall of the gut obliquely and there unite to form a short, dilated tube which is named the *hepatopancreatic ampulla* (*see* p. 1383). The narrow, distal end of this ampulla opens on the summit of a *major duodenal papilla*, which is situated within the descending part of the duodenum at the junction of its medial and posterior walls (**8**.113, 132), from 8 cm to 10 cm distal to the pylorus. The accessory pancreatic duct, when present, opens about 2 cm proximal to the major papilla, on a small rounded *minor duodenal papilla*.

The horizontal part (inferior or *third part*), about 10 cm long, begins at the right side of the lower border of the third lumbar vertebra and passes from right to left, with a slight inclination upwards, in front of the inferior vena cava, and ends in the fourth part in front of the abdominal aorta. Its anterior surface is covered with peritoneum, except near the median plane, where it is crossed by the superior mesenteric vessels and the root of the mesentery. Its posterior surface is uncovered by peritoneum, except towards its left extremity, where the left layer of the mesentery sometimes covers it to a variable extent. This surface rests upon the right ureter, the right psoas major, the right testicular (or ovarian) vessels, the inferior vena cava and the abdominal aorta (with the origin of the inferior mesenteric artery). The upper surface is in relation with the head of the pancreas; the lower, with the coils of the jejunum.

The ascending part (*fourth part*), about 2·5 cm long, ascends on or immediately to the left of the aorta, as far as the level of the upper border of the second lumbar vertebra, where it turns ventrally at the *duodenojejunal flexure* and is continuous with the jejunum. It lies in front of the left sympathetic trunk, left psoas major, the left renal and testicular vessels and the inferior mesenteric vein. Along its right border it gives attachment to the upper part of the root of the mesentery, the left layer of which is continued over its anterior surface and left side. To its left there are the left kidney and ureter; above, there is the body of the pancreas; in front, there is the transverse colon and transverse mesocolon (the latter separating the duodenojejunal flexure from the omental bursa and stomach).

The superior part of the duodenum, as stated above, is to a slight degree mobile, but the rest is relatively fixed, and is sessile upon neighbouring viscera and the posterior abdominal wall. Radiologically, after a barium meal, the superior part of the duodenum is seen as a somewhat triangular homogeneous shadow, called the 'duodenal cap' (**8**.108).

The terminal part of the duodenum and the duodenojejunal flexure are usually described as suspended and fixed in position by the '*suspensory muscle of the duodenum*' (suspensory muscle, or ligament, of Treitz). This is often said to be in two parts: (*a*) a slip of *striated* muscle, derived from the diaphragm near its oesophageal opening and ending in the connective tissue adjacent to the coeliac arterial trunk, and (*b*) a fibromuscular band, containing *nonstriated* muscle, which passes from the duodenum (third and fourth parts and duodenojejunal flexure) to blend with the same pericoeliac connective tissue. Treitz (1853) described both entities, naming the former one the *Hilfsmuskel* (accessory muscle). Some subsequent authorities (Lockwood 1886, and Low 1907) regarded these two structures as parts of a digastric muscle, naming the whole as the suspensory muscle of Treitz, a description perpetuated by many textbooks. The confusion was increased by Haley and Peden (1943), who derived the 'suspensory muscle' from the right crus, and by Argème *et al.* (1970), who described an intermediate tendon but regarded this as part of a 'false' digastric muscle. Jit (1952, 1977) has persistently supported the dual nature of the original description of Treitz, on embryological and histological grounds. The diaphragmatic slip (the Hilfsmuskel) has no satisfactory official name. It is supplied, according to Jit, by myelinated nerve fibres, derived probably from the phrenic nerve (pp. 550, 1094). This slip is sometimes considered to be an aberrant part of iliocostalis thoracis. The suspensory muscle proper (nonstriated) is supplied by autonomic fibres from the coeliac and superior mesenteric plexuses (Jit and Grewal, 1977). Descriptions of the extent of the duodenal attachments of the suspensory muscle vary; none of these accounts contain a convincing view of the function of the muscle, the usual suggestion being that it may kink the duodenojejunal flexure even further, producing a valvular effect.

Vessels and Nerves

The *arteries* supplying the duodenum are derived from the right gastric, supraduodenal, right gastro-epiploic and the superior and inferior pancreaticoduodenal arteries. (They are described on pp. 713, 716; **6**.86.) The superior part of the duodenum receives a leash of small branches from the hepatic artery proper which runs in the right part of the lesser omentum, and a similar leash of vessels from the gastroduodenal artery. These vessels also supply the neighbouring part of the pyloric canal, and there is some anastomosis in the wall of the alimentary canal between these vessels across the pyloroduodenal junction (p. 1338). The *veins* end in the splenic, superior mesenteric and portal veins. The *nerves* are derived from the coeliac plexus.

THE JEJUNUM AND ILEUM

The rest of the small intestine extends from the duodenojejunal flexure to the ileocaecal valve, where it ends in the junction of the caecum and ascending colon of the large intestine; it is arranged in a series of coils or loops which are attached to the posterior abdominal wall by its mesentery. This part of the gut is completely covered with the peritoneum, except for a narrow strip along its mesenteric border, where the two layers of the mesentery diverge from each other to enclose it. It is divided into jejunum and ileum, the former name being given to the first two-fifths and the latter to the distal three-fifths. There is no identifiable level of distinction between these two parts, and the division is arbitrary; but at the same time the character of the intestine gradually undergoes a change from the beginning of the jejunum to the end of the ileum, so that samples from these two situations present characteristic differences.

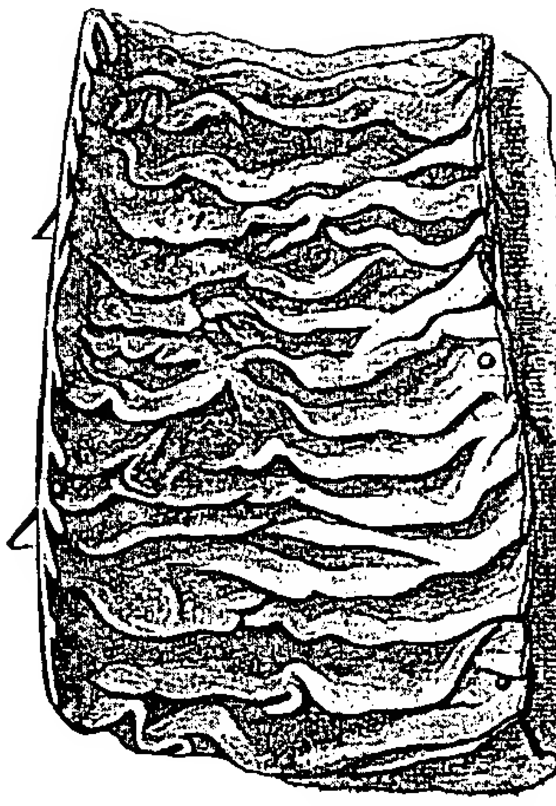
The jejunum has a diameter of about 4 cm, and is thicker, redder and more vascular than the ileum. The circular folds (p. 1345) of its mucous membrane are large and thickly set, and its villi surpass those of the ileum in size. The aggregated lymphatic follicles (p. 1349) are almost absent in the upper part of the jejunum; in the lower part they are fewer and smaller than in the ileum and tend to assume a circular form. When the jejunum is grasped between the finger and thumb the circular folds can be felt through the wall of the gut; as these folds are absent from the lower part of the ileum, it is possible in this way to distinguish the upper from the lower part of the small intestine.

For the most part the jejunum lies in the umbilical region, but it may extend into any of the surrounding areas. The first coil occupies a recess between the left part of the transverse mesocolon and the anterior surface of the left kidney.

The ileum has a diameter of 3·5 cm, and its wall is thinner than that of the jejunum. A few circular folds are present in the upper part of the ileum, but they are small and disappear almost entirely towards its lower end; the aggregated lymphatic follicles are, however, larger and more numerous than in the jejunum. For the most part the ileum is situated in the hypogastric (pubic) and pelvic regions. The terminal part of the ileum usually lies in the pelvis, from which it ascends over the right psoas major and right iliac vessels to end in the right iliac fossa by opening into the medial side of the junction of the caecum and ascending colon.

The jejunum and ileum are attached to the posterior abdominal wall by an extensive fold of peritoneum, termed the *mesentery*, which allows of very free movement, so that each coil can accommodate itself to changes in form and position.

The mesentery (p. 1329) is fan-shaped; its vertical border or root, about 15 cm long, is attached to the posterior abdominal wall along a line running from the left side of the body of the second lumbar vertebra to the right sacro-iliac joint, and crossing successively the horizontal part of the duodenum, the aorta, the inferior vena cava, the right ureter and right psoas major (**8**.98). Its average breadth from the vertebral to the intestinal border is about 20 cm, but is greater in the middle than at its upper and



8.115A Internal aspect of representative sample of proximal jejunum, showing circular folds.

lower ends. The two layers of the mesentery contain the jejunum, ileum, the jejunal and ileal branches of the superior mesenteric blood vessels, nerves, lacteals and lymph nodes, together with a variable amount of fat.

The diverticulum ilei (of Meckel) projects from the antimesenteric border of the lower part of the ileum in about 3 per cent of subjects. Its average position is about 1 m above the ileocaecal valve, and its average length about 5 cm. Its calibre is generally similar to that of the ileum, and its blind extremity may be free or may be connected with the abdominal wall or with some other part of the intestine by a fibrous band. It represents the persistent proximal part of the vitelline or yolk duct, which connects the yolk sac and the primitive digestive tube in early fetal life (pp. 120, 200, 205). The mucous membrane of the diverticulum usually has the same structure as that of the neighbouring ileum, but occasionally small regions of the mucous membrane may have a structure similar to that of the body and fundus of the stomach, with oxyntic cells which secrete acid. Sometimes small heterotopic areas of pancreatic or other tissues may be found in the wall of the diverticulum. In a recently published study of 1816 late fetal and neonatal cadavers Miyabara *et al.* (1974) found a diverticulum ilei present in 61 individuals (3·4 per cent). Of these, gastric mucosa was present in 11, jejunal mucosa in 2, colonic mucosa in 2, and pancreatic tissue in only 1.

STRUCTURE OF THE SMALL INTESTINE

The intestinal wall is composed of the series of layers described previously—serous, muscular, submucous and mucous (**8**.116).

The *serous layer* is formed of visceral peritoneum which merges with a subserous stratum of areolar connective tissue.

The *muscularis externa* is thicker in the cranial than in the caudal part of the small intestine; it consists of a thin outer longitudinal and a thick inner circular layer of nonstriated muscle fibres.

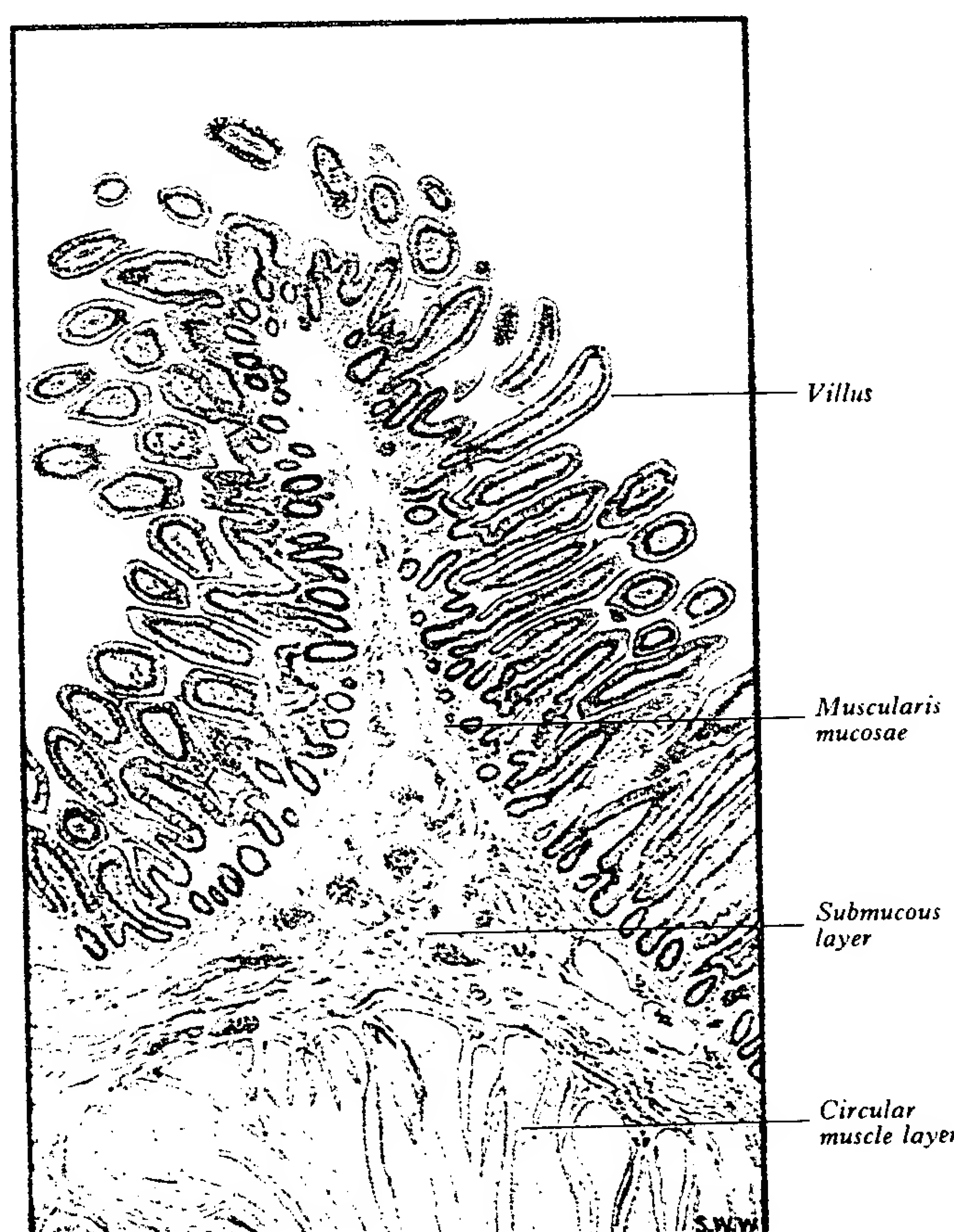
The *submucous layer* consists of loose connective tissue carrying blood vessels, lymphatics and nerves.

The *mucous membrane* is thick and highly vascular in the upper part of the small intestine, but thinner and less vascular in the lower part. It is thrown into circular or spiral pleats or plicae, the *circular folds*, and the whole surface is studded with finger-like, filiform or tongue-shaped projections, the intestinal villi.

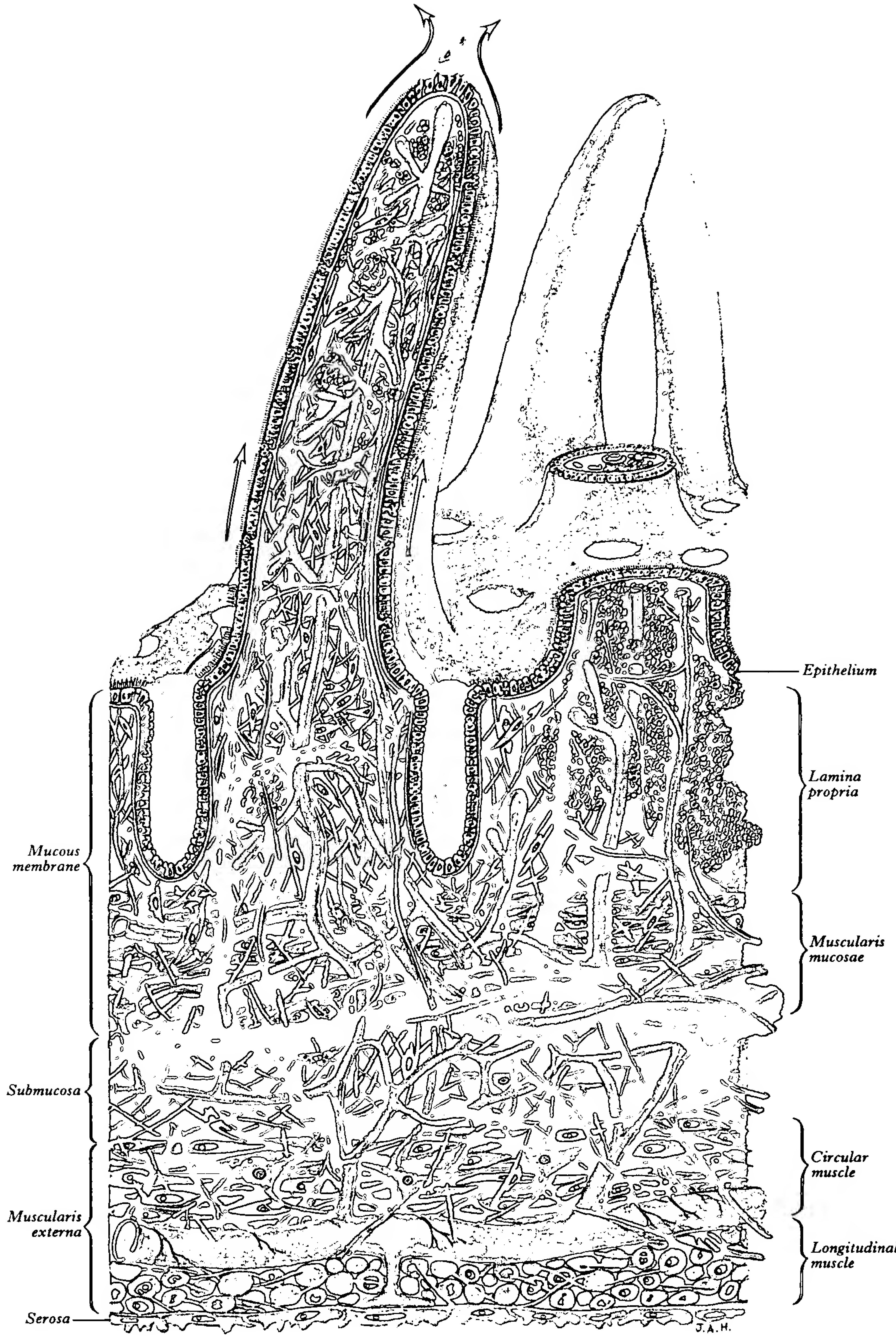
The circular folds (*plicae circulares*, or '*valves*' *of Kerkring*—**8**.115, 119), are large, crescentic folds of mucous membrane which project into the intestinal lumen transversely to its long axis. Unlike the folds in the stomach they are permanent: they are not obliterated when the intestine is distended. The majority extend round the intestine for about one-half or two-thirds of its circumference, but some form complete circles, some bifurcate and join adjacent folds, and others have a spiral direction; the latter usually extend a little more than once round the lumen, but occasionally two or three times. The larger folds are about 8 mm in depth at their broadest part; but the greater number are of smaller size. The larger and smaller folds often alternate. Circular folds do not exist in the commencement of the duodenum, but begin to appear about 2·5 to 5 cm beyond the pylorus. Distal to the point where the common bile duct (ductus choledochus) and pancreatic duct enter the duodenum, the folds are very large and closely approximated. In the proximal half of the jejunum they are large and numerous, but from here to a point midway along the ileum, they diminish considerably in size. In the distal ileum they are almost entirely absent; hence the comparative thinness of this portion of the intestine, as compared with the duodenum and jejunum. The circular folds retard the passage of the food and afford an increased surface for absorption (**8**.119).

The intestinal villi are highly vascular processes, just visible to the naked eye; they project from the mucous membrane of the whole of the small intestine, and give to its surface a velvety appearance. They are large and numerous in the duodenum and jejunum, but are smaller and fewer in the ileum. In the first part of the duodenum they are broad, ridge-like structures, changing to tall leaf-like villi in the distal duodenum and proximal jejunum thereafter they gradually transform into shorter finger-like extensions in the distal jejunum and ileum (Verźar and McDougall 1936; McMinn and Mitchell 1954). They vary in density from 10 to 40 per square millimetre, and are from about 0·5 to 1·0 mm in height. The villi increase the surface area, compared with an unfolded surface, about eightfold. (For details of an experimental analysis of the formation of intestinal villi after lesions of the mucosa in the small intestine of the cat, consult McMinn and Mitchell 1954.)

The mucous membrane (**8**.116) of the small intestine has three layers. Next to the submucous coat is the *muscularis mucosae* which consists of an outer longitudinal and an inner circular layer of nonstriated muscular fibres. This layer extends into the circular folds. Internal to it is a quantity of reticular tissue, the lamina propria, in which, in addition to fibroblasts and fibres, there are lymphocytes, eosinophilic leucocytes, macrophages,



8.115B Section through a circular fold from human small intestine. Stained with haematoxylin and eosin. Magnification about × 19.



8.116 A three-dimensional reconstruction of the architecture of intestinal villi and subjacent wall; the principal layers of the latter are indicated. Arteries and arterioles—red; veins and venules—blue; central lacteals and other lymphatic channels—orange; aggregations of lymphocytes—yellow; neural elements—green; nonstriated muscle fibres—magenta; fibroblasts—white. Note the orifices of the intestinal crypts (of Lieberkühn). Types of cells in the epithelium include absorptive cells, goblet cells, and entero-endocrine cells. Arrows indicate direction of cell migration. The various layers are not drawn to scale.

8.117A A light micrograph of part of the mucosa of the murine small intestine, showing a villus in longitudinal section. Nonstriated myocytes (pink) can be seen in the lamina propria of the villus. Stained with haematoxylin, eosin, and periodic acid/Schiff. (Prepared and photographed by Mr. Stephen Sitch, Department of Anatomy, Guy's Hospital Medical School, London.) Magnification about ×250.

mast cells, blood capillaries, lymphatic vessels and nonmyelinated nerves. The plasma cells are numerous and the lymphocytic cells are in many regions collected into solitary and aggregated lymphatic follicles, some of which may extend through the muscularis mucosae into the submucous coat. Internal to the lamina propria is a basement membrane supporting an epithelium composed mainly of tall columnar cells, except over lymphatic follicles where they are partly replaced by *membrane* or *M cells*, specialized for transport of antigens (Owen and Nemamic 1978). Extending into the mucosa from the surface between the intestinal villi are simple, tubular, *intestinal glands* or *crypts* (of *Lieberkühn*). They reach almost to the muscularis mucosae. In the duodenum there are also mucous, tubulo-alveolar *duodenal glands* (of *Brunner*), the ducts of which extend through the muscularis mucosae to expand into the submucous coat; the secretions of these glands contain mucosubstances and bicarbonate ions.

Structure of the Intestinal Villi

Each villus has a core of reticular tissue containing a lymph vessel or lacteal, blood vessels, nerves and some nonstriated muscle fibres covered by a layer of columnar epithelium resting on a basement membrane (8.116, 117A–D).

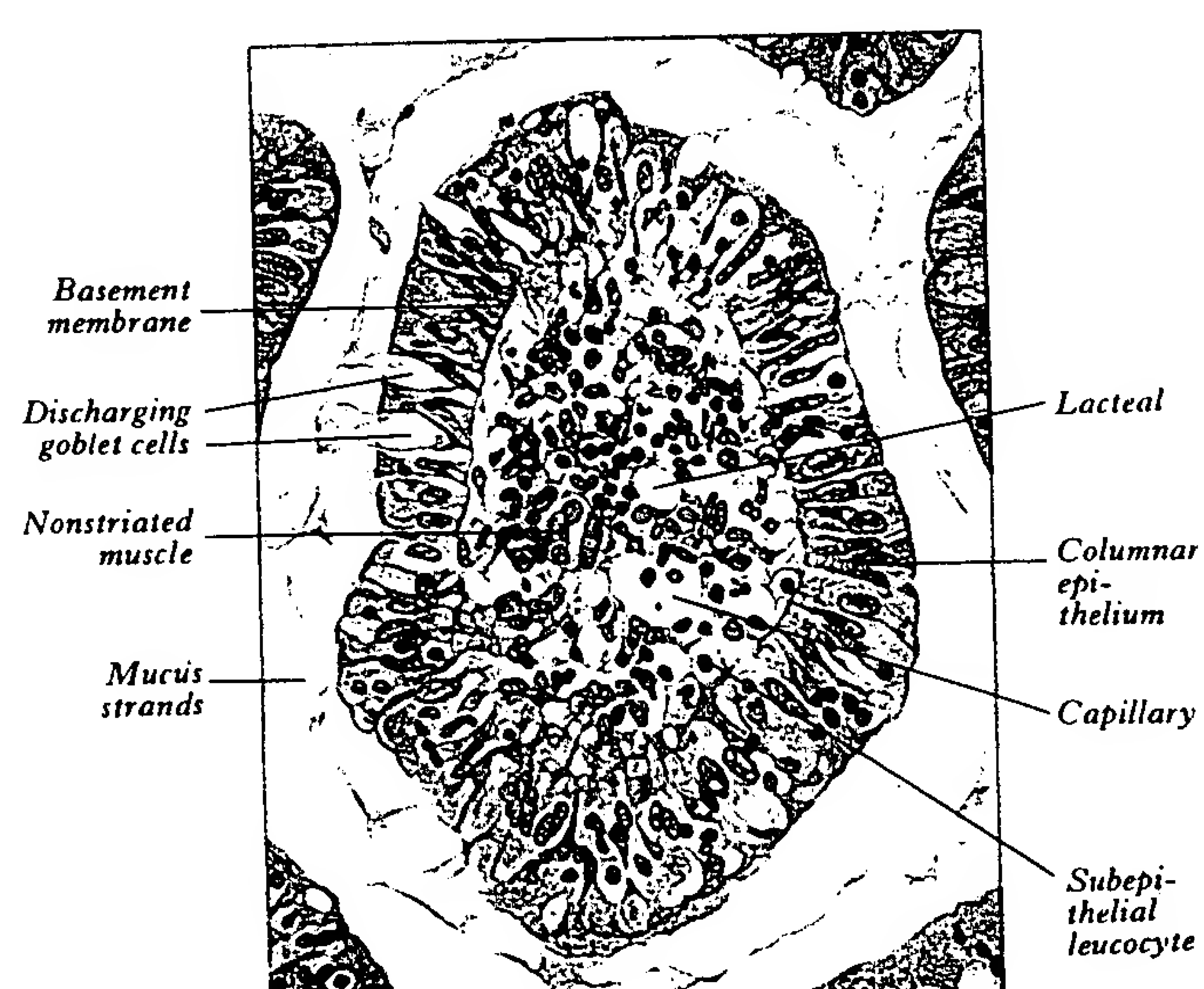
The *lacteal*, usually single but occasionally double, commences in a dilated blind extremity near the summit of the villus and then courses along the axis of the villus and empties into the plexus of lymph vessels in the underlying lamina propria. Its wall is composed of a single layer of endothelial cells.

The *muscle fibres* are derived from the muscularis mucosae, and are arranged in bundles around the lacteal vessel, extending from the base to the summit of the villus, and giving off, laterally, individual muscle cells, which are enclosed by the reticulum, and by it are attached to the basement membrane and to the lacteal. Contraction of the muscularis mucosae therefore has the effect of 'milking' the lacteals.

The *blood vessels* form a capillary plexus in the lamina propria, and are enclosed in the reticular tissue. The capillaries are lined by a fenestrated endothelium, a modification which may be of considerable importance in ensuring the rapid uptake of nutrients diffusing from the epithelium (Clementi and Palade 1969).

The *epithelium* covering the superficial surface of the mucous membrane and the intestinal villi consists mainly of absorptive columnar cells, interspersed with goblet cells.

The columnar cells (1.1) are granular in appearance; each possesses a clear oval nucleus located in its basal half. At the free surface of the cell there is a highly refractile, vertically striated border about 1 μm in depth, the *striated* or *brush border*. This border is very rich in alkaline phosphatase and is concerned with the process of active absorption; electron microscope studies show that this border is composed of minute parallel cylindrical microvilli, each about 1 μm long and 0·1 μm broad. Applied to the outer surface of the enveloping plasma membrane of the microvilli is a coating of ultramicroscopic fine filaments, rich in mucosubstances, believed to be formed by the epithelial cells and to constitute an integral part of the surface. In the cytoplasmic core of each microvillus are fine filaments which are continuous at its base with a plexiform band of similar filaments in the apical cytoplasm of the cell; this band is the *terminal web* and, except for occasional vesicles, is free of organelles (8.118B). The lateral plasma membranes of the columnar cells are often plicated and interdigitated; at their luminal extremities they show typical junctional complexes (p. 7, 1.4). Elsewhere scattered desmosomes occur between adjacent plasma membranes; basally, the lateral plasma membranes may be separated by intervals constituting intercellular canaliculi. The basal plasma membranes are usually smooth and lie adjacent to the basement membrane which is about 20 nm wide. Rod-shaped mitochondria are scattered through the cell cytoplasm together with a moderate amount of rough and smooth surfaced endoplasmic reticulum. The Golgi apparatus is supranuclear in position and the apical part of the cell, beneath the terminal web, contains numerous membrane-bound lysosomes. At the summits of the intestinal villi the cells often show signs of degeneration and their microvilli may be stunted and degenerate. The role of these cells in digestion and absorption of nutrients has attracted much attention. It appears likely that absorption of amino acids and simple carbohydrates occurs by facilitated diffusion across the cell membranes, these materials passing

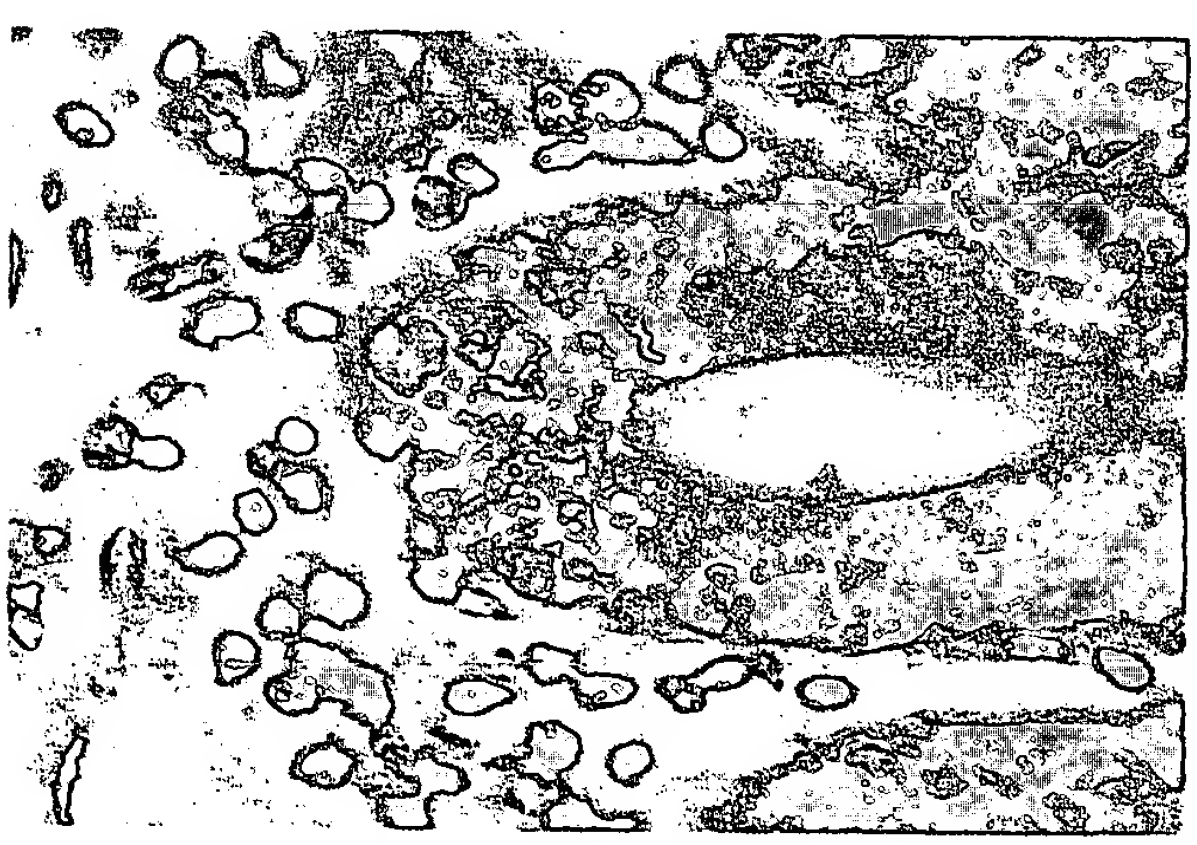


8.117 B Transverse section through a villus in human jejunum. Stained with haematoxylin and eosin. Magnification about ×380.

through the cell to the underlying capillary arrays of the lamina propria. Lipid absorption also appears to occur by the diffusion of small molecules (fatty acids, etc.) through the membrane of the luminal surface, the lipid accumulating in the vacuoles within the cytoplasm in the apical region of the cell, before being passed to the underlying lymphatics. It has also been possible to isolate the striated borders of absorptive cells by cell fractionation and centrifugation; digestive enzymes such as disaccharidases are bound to the surface, and there are indications that much of the intestinal digestion may occur close to the site of absorption, digestive enzymes being absorbed on to the cell surfaces, perhaps in the polysaccharide cell coat.

The goblet cells are intercalated at intervals in the epithelial layer. Their nuclei are elongated and basally situated and their apical parts are distended with membrane-bound mucin granules. The Golgi apparatus is well developed and supranuclear in position and the granular endoplasmic reticulum is abundant infranuclearly. The goblet cells have less frequent and more irregular microvilli at their superficial surfaces and the terminal web is poorly marked. The mucin is believed to be generally

8.117 C Intestinal glands and villi in human small intestine. Stained with haematoxylin and eosin. Magnification about × 120.



8.117 D Part of a transverse section of the ileum, showing Paneth cells containing orange-stained zymogen granules at the base of an intestinal gland. 'Undifferentiated' epithelial cells are also visible. Mallory's azan stain. Magnification about × 400.

discharged by fusion of the membranes surrounding the granules with the plasma membrane in the manner of a merocrine secretion (8.118A).

The intestinal glands (*crypts of Lieberkühn*) occur in considerable numbers over every part of the mucous membrane of the small intestine. They are simple tubular pits, arranged perpendicularly to the surface, upon which they open by small circular apertures. Their orifices may be seen with the aid of a lens as minute dots scattered between the villi. Their walls are thin, consisting of columnar epithelium on a basement membrane and associated with a rich mucosal capillary plexus (8.116).

The cells lining the intestinal glands consist of so-called 'undifferentiated cells', Paneth and argentaffin cells. **The undifferentiated cells** are the most numerous and proliferate by mitotic division, passing upwards out of the intestinal glands along the sides of the villi, where they differentiate into columnar absorptive elements or into goblet cells; eventually they reach the tips of the villi, from which they are shed. In this way there is a continual renewal of the epithelial covering of the villi. When not dividing, the free surfaces of these cells have fewer and more irregular microvilli than the surface cells with occasional pseudopodia; their lateral plasma membranes are straighter but the attachment areas are similar in both types of cell. Their nuclei are basally placed and the terminal webs are poorly developed. Membrane-bound secretory granules occur in their cytoplasm and are believed to be discharged both in the manner of an apocrine secretion through the surface blebs and by the more usual merocrine mechanism commonly described. The undifferentiated epithelial cells in the intestinal glands multiply at the rate of 1 cell per 100 cells per hour and constitute one of the most rapidly proliferating of tissues in the body (Lipkin *et al.* 1963, MacDonald *et al.*, 1964).

The zymogenic cells (of Paneth) are numerous in the deeper parts of the intestinal crypts, particularly those of the duodenum. They are rich in zinc and contain granules (8.117D) which stain with phosphotungstic haematoxylin. Electron microscopy shows irregular microvilli to be present at the apices of these cells, and prominent membrane-bound granules to be present in the supranuclear cytoplasm. Scattered mitochondria, lysosomes and a large amount of granular endoplasmic reticulum also exist, especially in the basal parts of the cells. These zymogenic cells are the source of the digestive enzymes produced by the wall of the small intestine.

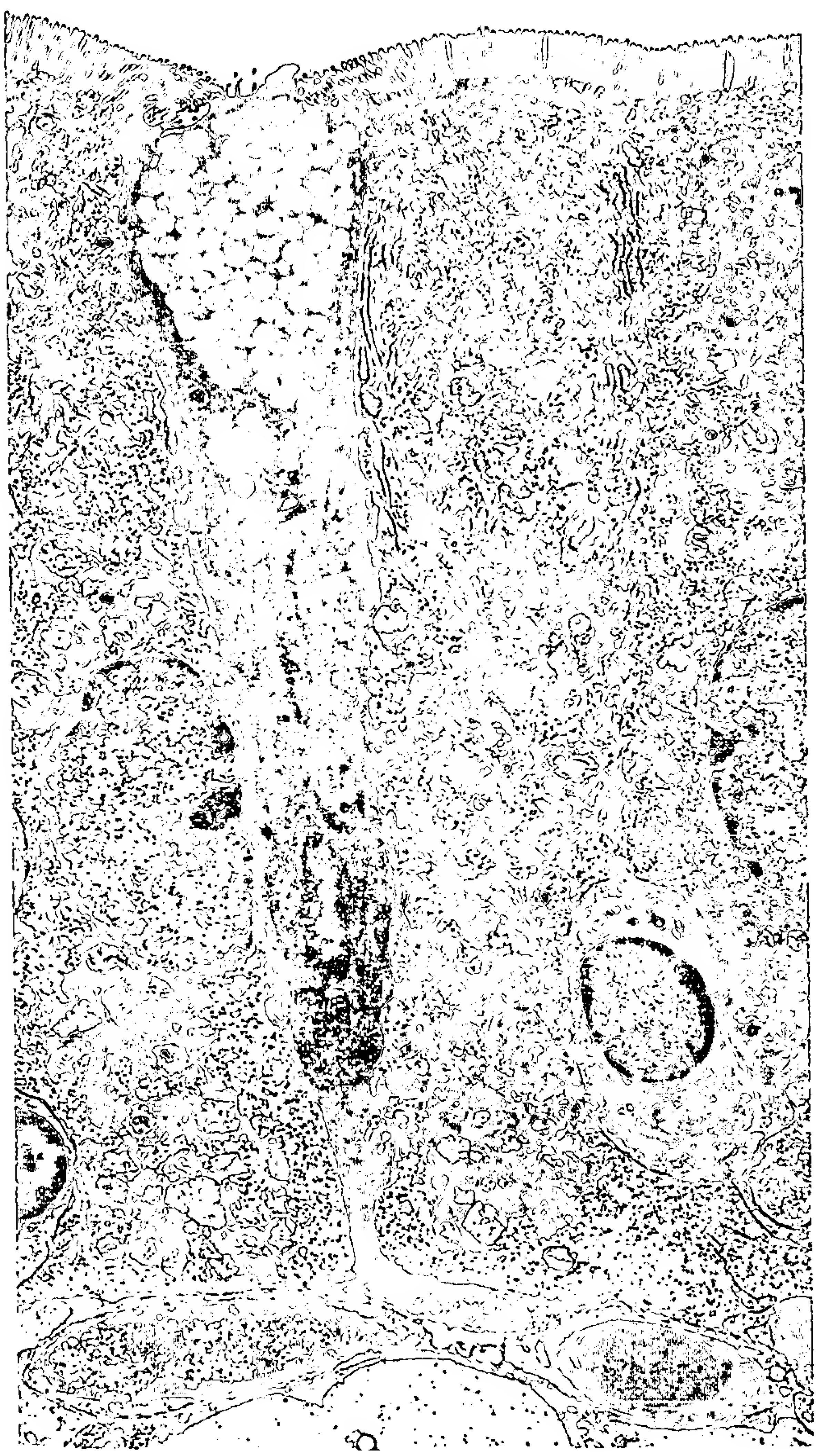
Between the cells lining the intestinal glands, and less commonly among those covering the villi, are pyramidal or columnar cells, the cytoplasm of which contains granules that have an affinity for silver salts, by which they are stained black, and for chromium salts, by which they are stained brown. They are called **enterochromaffin cells** or **argentaffin cells** and are a variety of APUD cell (*see* p. 1366). The distributions of these and other cells of the gastro-entero-pancreatic endocrine system are shown in 8.129C.

The duodenal glands (of Brunner) are limited to the duodenum (8.114), and are sited *in the submucous areolar tissue*, i.e. they penetrate through the muscularis mucosae. They are largest and most numerous near the pylorus, forming an almost complete layer in the superior part and proximal half of the descending part of the duodenum; beyond this they gradually diminish in number and disappear at the junction of the duodenum and jejunum. They are small, compound, acinotubular glands, each consisting of a number of alveoli lined with short columnar epithelium and opening by a duct on the inner surface of the intestine. They seemingly contain only one kind of exocrine cell in man; this is a typical mucous element. The nuclei of these cells are small and basal, and they show variations according to the secretory cycle. The Golgi apparatus is extensive; mucin droplets are numerous. Many argentaffin cells (*vide supra*) are present amongst the mucinogenic cells.

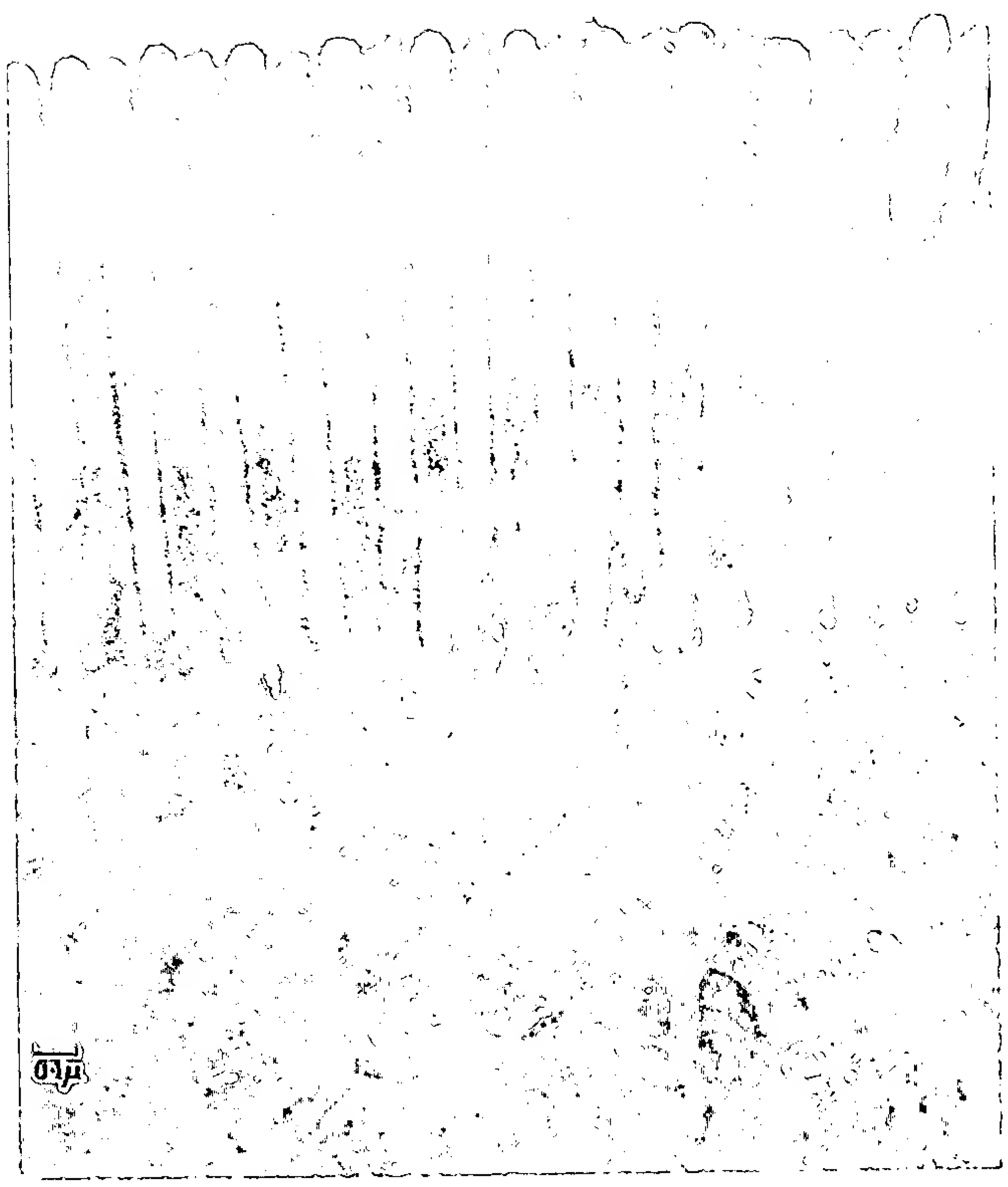
The solitary lymphatic follicles are seen to be scattered throughout the mucous membrane of the small intestine but are most numerous in the lower part of the ileum. Their free surfaces are covered with rudimentary villi, except at the summits, and each follicle is surrounded by the openings of the intestinal glands. Each consists of a dense, interlacing, reticular tissue

closely packed with lymphocytes, and permeated by an abundant, capillary network. The interspaces of the reticular tissue are continuous with larger lymph spaces which surround the follicle, and by this means they are enabled to communicate with the lacteal system. They are situated partly in the submucous tissue and partly in the mucous coat. They are partly covered by 'M' cells p. 1347

The aggregated lymphoid follicles (Peyer's patches, 8.120A, B) form circular or oval patches, individual ones containing from 10 to 260 follicles, and varying in length from 2 to 10 cm. Like the other collections of lymphoid tissue in the body (except the lymph nodes), solitary and aggregated lymphatic follicles are most numerous around puberty and thereafter diminish in number and size but many persist to old age (Cornes 1965). Aggregated follicles are largest and most numerous in the ileum. In the distal part of the jejunum they are small, circular and few in number. They are occasionally seen in the duodenum. They are placed lengthwise in the intestine, and are in the part of its circumference most distant from the attachment of the mesentery. Each patch is formed of a group of solitary lymphoid



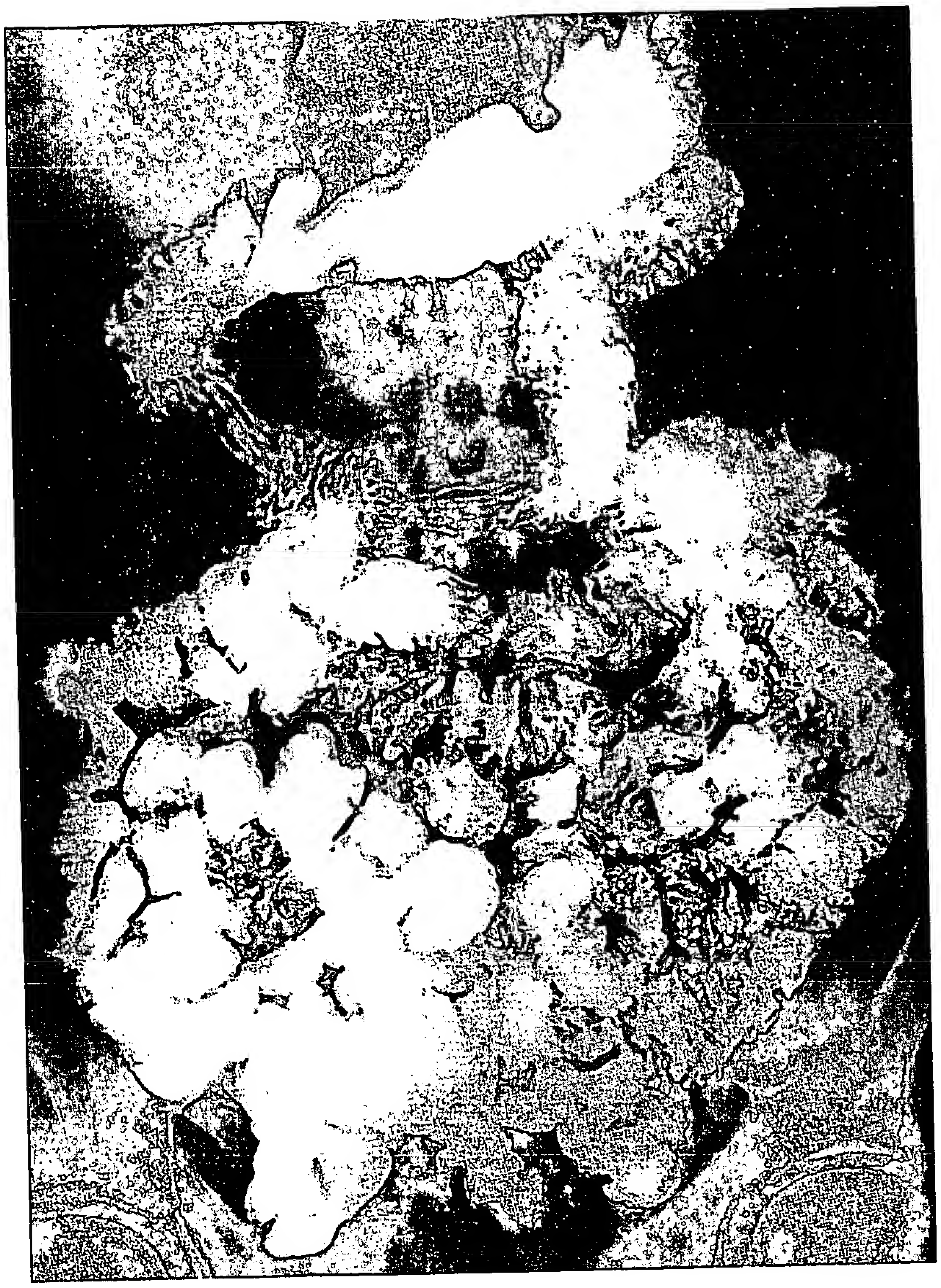
8.118A Transmission electron micrograph of the columnar epithelium lining the murine small intestine, showing a mucus-secreting goblet cell between two absorptive cells which bear microvilli. The cells rest on a delicate basal lamina deep to which is the vascular lamina propria. (Magnification × 4,800.) (Prepared and photographed by Mr. Derrick J. Lovell, Department of Anatomy, Guy's Hospital Medical School, London.)



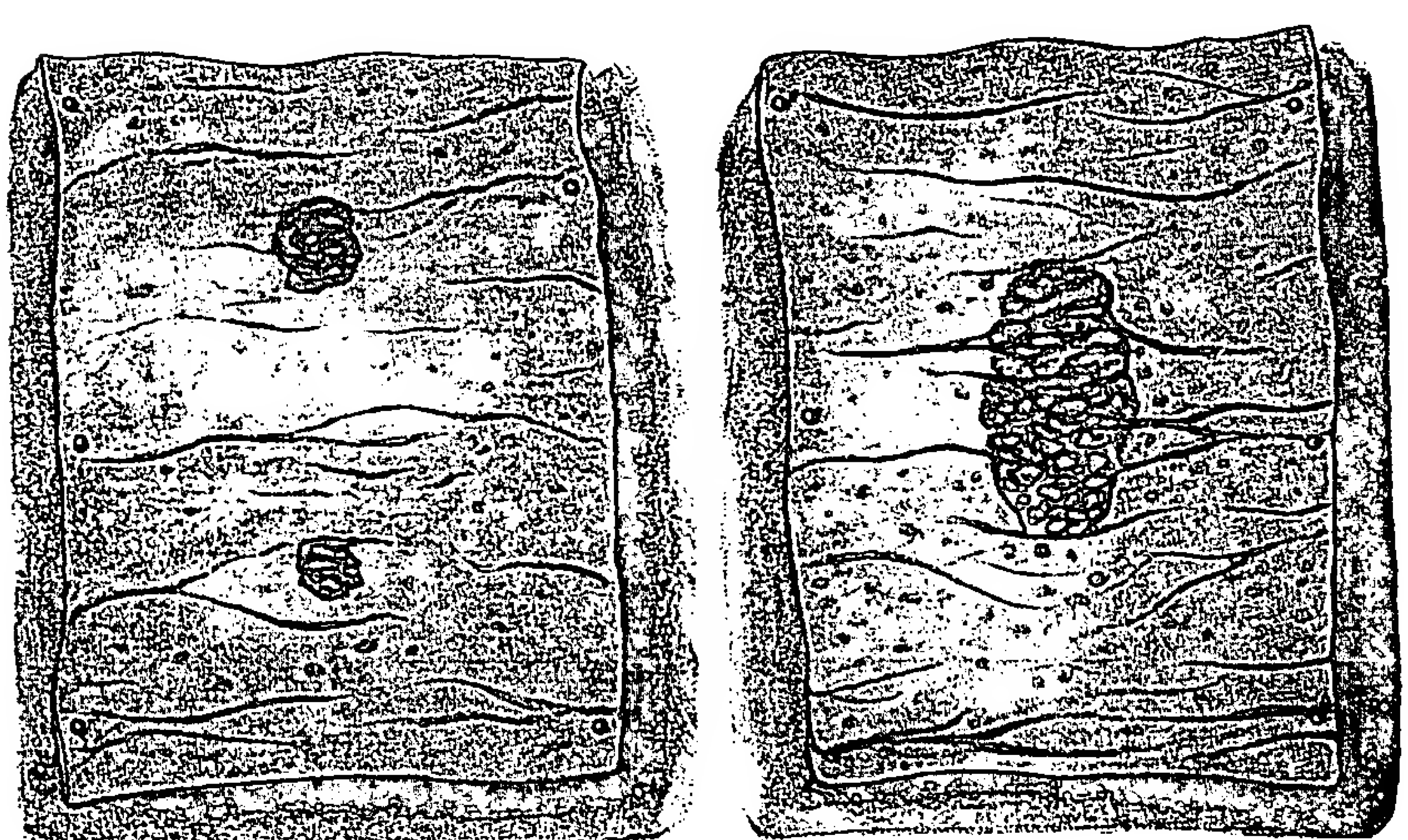
8.118B Electron micrograph of the apical region in a columnar cell from the jejunum showing the regular series of microvilli which constitutes the striated border of light microscopy. Filaments can be seen passing from the microvilli to the terminal web. Rat. Magnification about × 32,500.

follicles covered with columnar epithelial cells and 'M' cells (p. 1347); the patches do not, as a rule, possess villi on their free surfaces. They are freely supplied with blood vessels, which form an abundant plexus around each follicle and give off fine branches to permeate the lymphoid tissue in the interior of the follicle. The plexuses of lymph vessels are especially abundant around these patches. In typhoid fever, ulceration of these aggregated lymphatic follicles may occur; the ulcers are thus oval in shape, their long axes are in the long axis of the bowel (so subsequent fibrosis does not constrict the gut), they are present chiefly in the lower part of the ileum, and are situated on or near its antimesenteric border.

Vessels and nerves. The *arteries* to the jejunum and ileum (8.120C, D) stem from the superior mesenteric artery, the jejunal and ileal branches of which, having reached the mesenteric border extend between the serous and muscular coats. From these vessels numerous branches are given off, which pierce the muscular coat, supplying it and forming an intricate plexus in the submucous tissue. From this plexus minute vessels pass to the glands and villi of the mucous membrane (*see* p. 1347). The anastomoses between the terminal intestinal branches are by no means free, and there is a distinct tendency for the alternate vessels to be distributed to opposite sides of the gut. The *veins* have a course and arrangement similar to the arteries. (For an extensive and detailed investigation into the course, distribution and variations in the coeliac and superior mesenteric arteries consult Nesebar *et al.* 1969.) The *lymph vessels* of the small intestine (lacteals) are arranged in two sets, viz. those of the mucous membrane and those of the muscular coat. The lymph vessels of the villi commence in these structures in the manner described on p. 1347. They form a highly intricate plexus in the mucous and submucous tissue, being joined by the lymph vessels from lymph spaces at the bases of the solitary follicles, and from there pass to larger vessels at the mesenteric border of the gut. The lymph vessels of the muscular coat are situated to a great extent between the two layers of muscular fibres, where they form a close plexus; throughout their course they communicate freely with those from the mucous



8.119 A radiograph of the pyloric end of the stomach, duodenum, jejunum and ileum, one hour after taking a barium meal. The feathery appearance of the profile of the small intestine is due to the presence of numerous circular mucosal folds.



8.120A and B Aggregated lymphatic follicles, in the proximal (A) and distal (B) parts of the ileum.

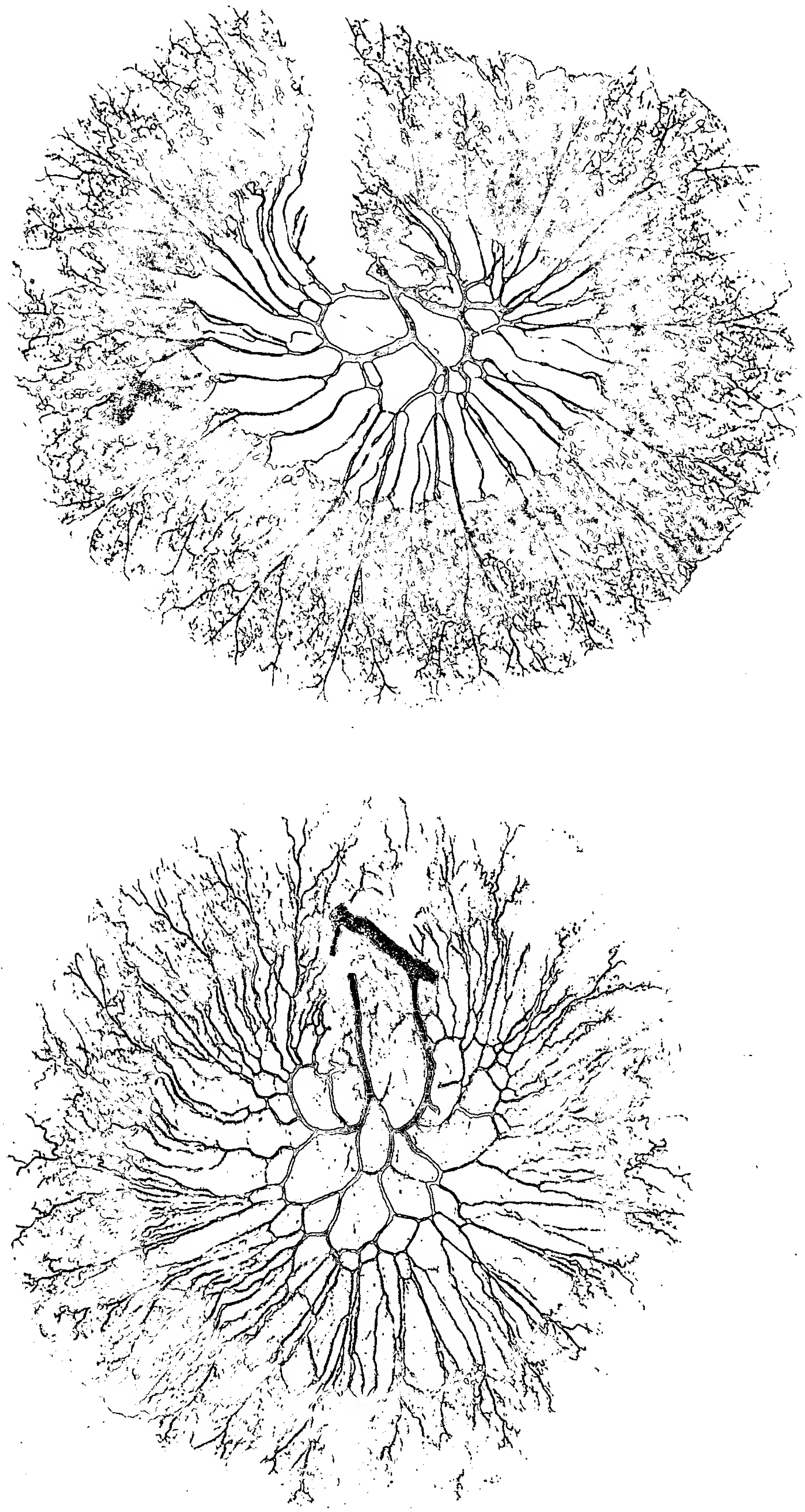
membrane, and open in the same manner as these into the origins of the lacteal vessels at the attached border of the gut.

The *nerves* of the small intestine are derived from the vagus and splanchnic nerves through the coeliac ganglia and the plexuses around the superior mesenteric artery. They run to the *myenteric plexus* (p. 1316) of nerves and ganglia, situated between the circular and longitudinal layers of the muscularis externa, which they supply. From the myenteric plexus a secondary plexus, termed the *submucous plexus*, is derived, and is formed by branches which have perforated the circular muscular layer. This plexus also contains ganglionic neurons from which the nerve fibres pass to the muscularis mucosae and to the mucous membrane. The nerve bundles of the submucous plexus are finer than those of the myenteric plexus. The neurons in both plexuses are essentially parasympathetic (vagal). An old controversy as to the source of the postganglionic neurons in the enteric ganglia has been renewed latterly (Andrew 1971). Endodermal and mesodermal origins have been suggested, but the evidence (though largely equivocal) indicates a derivation from the neural crest. In general the sympathetic is inhibitory to the peristaltic movements of the alimentary canal, but stimulates the sphincters and also the muscularis mucosae. While the parasympathetic is generally an augmentor of the peristaltic movements and an inhibitor of the sphincters, the result of stimulation of the parasympathetic appears to depend on the state of contraction or relaxation of the organ at the time of stimulation. The parasympathetic is also augmentory to the intestinal secretion. For an extensive evaluation of the status of the 'intestinal' cells (of Cajal) in the intestinal wall, consult Rogers and Burnstock (1966). It seems probable that these are connective tissue cells, and not neurons. There is some evidence that some of the neurons in the ganglia of the intestinal wall may be afferent (Fehér and Vajda 1974).

The Large Intestine

The large intestine extends from the end of the ileum to the anus, and is about 1·5 m long. Its calibre is greatest at its commencement at the caecum, and gradually diminishes as far as the rectum, where there is a dilatation of considerable size just above the anal canal. Its functions being chiefly the absorption of fluid and solutes, it differs considerably in appearance, structure, size and arrangement from the small intestine. (1) It has a greater calibre. (2) For the most part, it is more fixed in position. (3) Its longitudinal muscular fibres, although distributed as a *complete* layer, are particularly concentrated to form three longitudinal bands or *taeniae coli*. (4) Since these taeniae are often held to be 'shorter' than the circular muscular coat, the intervening colonic wall is puckered and thrown into *sacculations* (alternatively termed *haustrations*). It is not certain that the sacculation is adequately explained in this manner (*see* p. 1362, and Hamilton 1946; Pace 1968). (5) Small, peritoneum-covered, adipose projections, termed *appendices epiploicae*, are found scattered over the free surface of the whole of the large intestine, with the exceptions of the caecum, the vermiform appendix and the rectum.

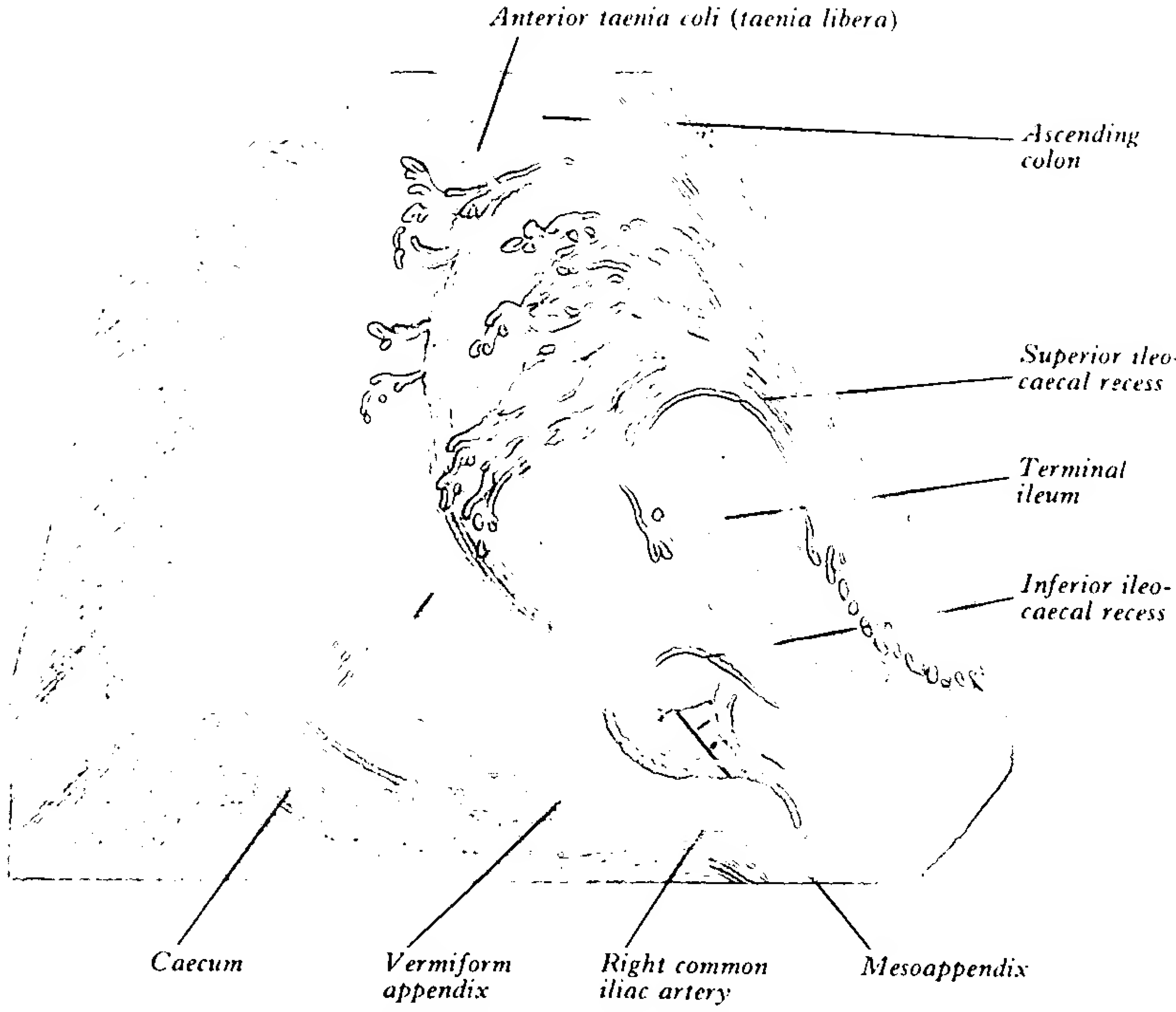
In its course the large intestine curves around and usually encloses the convolutions of the small intestine. It commences in the right iliac region, in a dilated part termed the *caecum* (*intestinum crassum caecum*—the term *caecum*, like rectum, duodenum and others, is an adjective, rapidly becoming by linguistic abbreviation a noun). The colon ascends the right lumbar and hypochondriac regions to the inferior surface of the liver; here it bends (the *right colic flexure*, **8**.111) to the left, and, curving with a downward and a forward convexity, passes, as the *transverse colon*, across the abdomen to the left hypochondriac region; it then bends again (the *left colic flexure*, **8**.111), and descends through the left lumbar and iliac regions to the lesser pelvis, where it forms a sinuous loop, the *sigmoid colon* (**8**.125); from this it is continued along the lower part of the posterior wall of the pelvis as the rectum and anal canal. It is divided into the caecum (including the vermiform appendix), the colon, the rectum and the anal canal.



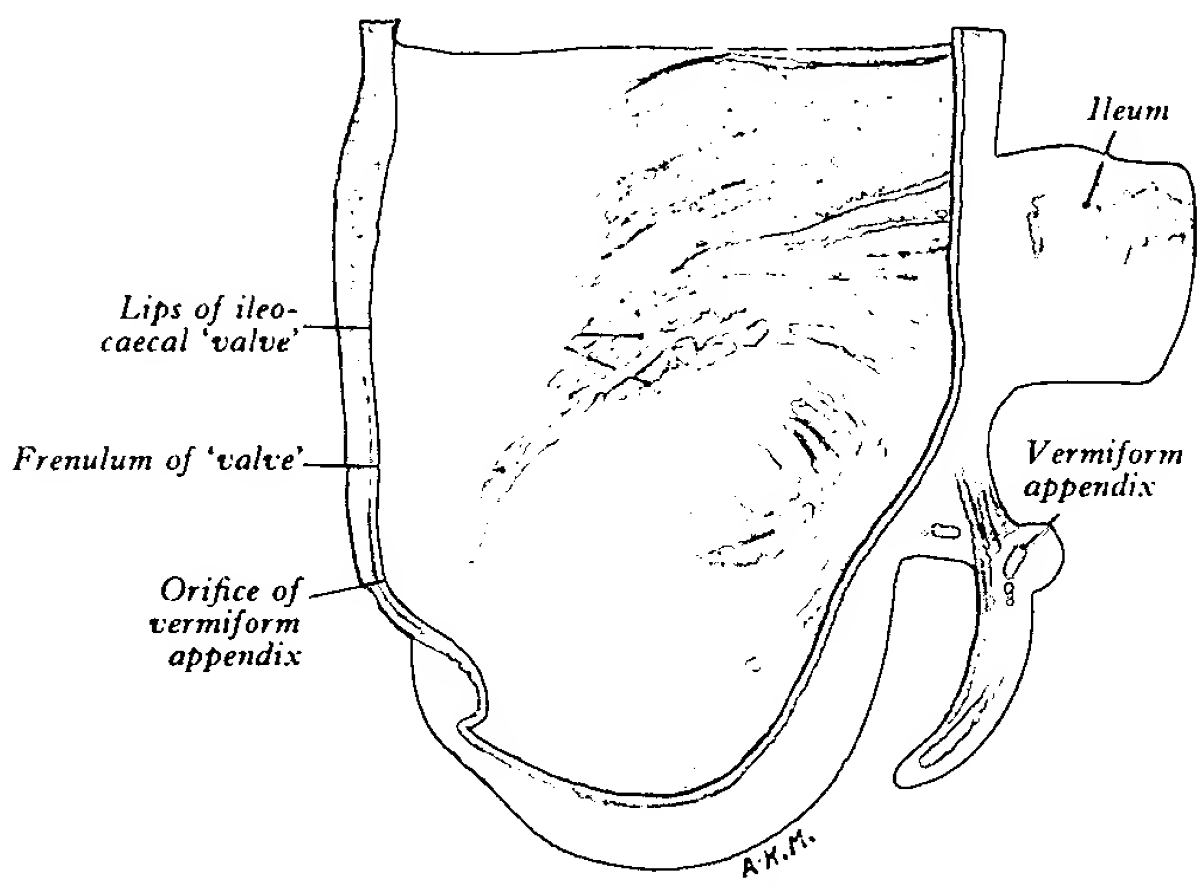
C

D

8.120C and D Specimens of the jejunum (C) and ileum (D) from a subject in whom the superior mesenteric artery was injected with a red coloured mass of gelatin before fixation. Subsequently the specimens were dehydrated, and then cleared in benzene followed by methyl salicylate. The largest vessels present are the jejunal and ileal branches of the superior mesenteric artery, and these are succeeded by anastomotic arterial arcades, which are relatively few in number (1–3) in the jejunum, becoming more numerous (5–6) in the ileum. From the arcades, straight arteries pass towards the gut wall; frequently, successive straight arteries are distributed to opposite sides of the gut. Note the denser vacularity of the jejunal wall. (Specimens prepared by Dr. Michael C. E. Hutchinson, Department of Anatomy, Guy's Hospital Medical School.)



8.121A The terminal ileum, caecum and vermiform appendix. Anterior aspect.



8.121B The interior of the caecum and commencement of the ascending colon, showing the ileocaecal 'valve'. (See text for discussion.)

THE CAECUM

The caecum (8.121A, B), the commencement of the large intestine, is in the right iliac fossa—its surface projection hence occupies the triangular area bounded by the right lateral plane, the transtubercular plane and the inguinal ligament. It is a large cul-de-sac continuous superiorly with the ascending colon, and at the point where the one passes into the other the ileum opens into the large intestine from the medial side. Its average axial dimension is about 6 cm and its breadth about 7·5 cm. In the right iliac fossa it is superior to the lateral half of the inguinal ligament: it rests posteriorly on the iliacus and on the psoas major, being separated from both muscles by their covering fasciae and the peritoneum, and posterior to it is the *retrocaecal recess* (p. 1331) which frequently contains the vermiform appendix. In addition, the lateral cutaneous nerve of the thigh intervenes between it and the iliacus. Anteriorly it is usually in contact with the anterior abdominal wall, but the greater omentum, and, if the caecum is empty, some coils of small intestine may be interposed. Usually, it is entirely enveloped by peritoneum, but sometimes the peritoneal covering is incomplete, the superior part of its posterior surface being uncovered and sessile, connected to the iliac fascia by areolar tissue. Commonly, however, the caecum enjoys a considerable amount of movement, so that it may even become herniated through the right inguinal canal. It is also commonplace to deliver the caecum through an appropriate incision in the anterior abdominal wall during the course of an appendicectomy.

Caecal Variations

The caecum varies in shape, and it has been classified under one of four types (Treves 1885). In early fetal life it is short, conical and broad at the base, with its apex turned upwards and medially towards the ileocaecal junction. As the fetus grows, the caecum increases in length more than in breadth, so that it forms a longer tube and lacks the broad base, but still has the same inclination of the apex towards the ileocaecal junction. As development continues, the lower part of the tube ceases to grow and the upper part becomes increased, so that at birth the narrow vermiform appendix extends from the apex of a conical caecum. This is the *infantile form* and as it persists throughout life in about 2 per cent of subjects, it was regarded by Treves as the *first* of his four types of human caeca. The three taeniae coli (p. 1362) start from the appendix and are equidistant from each other. In the *second* type, the conical caecum has become quadrate by the outgrowth of a saccule on each side of the anterior taenia. These saccules are of equal size, and the appendix arises from the depression between them, instead of from the apex of a cone. This type is found in about 3 per cent of subjects. The *third* type is the normal type for man. Here the two saccules, which in the second type were uniform, have grown at unequal rates, the right with greater rapidity than the left. In consequence of this an apparently new apex has been formed by the downward growth of the right saccule, and the original apex, with the appendix attached, is pushed over to the left towards the ileocaecal junction. The three taeniae still start from the base of the vermiform appendix, but they are now no longer equidistant from each other, because the right saccule has grown between the anterior and posterolateral taeniae, pushing them over to the left. This type occurs in about 90 per cent of subjects. The *fourth* type is merely an exaggerated condition of the third; the right saccule is still larger, and at the same time the left saccule has become atrophied, so that the original apex of the caecum, with the vermiform appendix, is close to the ileocaecal junction, and the anterior taenia courses medially to the same situation. This type is present in about 4 per cent of subjects.

In a more recent study (Pavlov and Pétrov 1968) covering eighty-two males and forty-four females (adolescent and adult), the third type noted above was designated *ampullary*, and this accounted for 78 per cent. A so-called *infundibular* type, approximating to the conical group, occurred in 13 per cent. The remaining 9 per cent were intermediate. In the same series, the caecum was mobile 20 per cent more often in females. (For further developmental analyses consult Balthazar and Gade 1976.)

THE ILEOCAECAL VALVE

The lower end of the ileum opens into the medial and posterior aspect of the large intestine, at the point of junction of the caecum with the colon (8.121B). The ileocaecal orifice is represented on the surface at the point of intersection of the right lateral and transtubercular planes; about 2 cm below this point the vermiform appendix opens into the caecum. The opening is provided with a so-called 'valve', consisting of two segments or flaps which project into the lumen of the large intestine. *After inflation and fixation* of the caecum, the flaps are of a semilunar shape. The upper, approximately horizontal, is attached to the line of junction of the ileum with the colon; the lower, which is longer and more concave, is attached to the line of junction of the ileum with the caecum. At the ends of the aperture the two segments of the valve coalesce, and are continued as narrow membranous ridges for a short distance, forming the *frenula* of the valve. The left or anterior end of the aperture is rounded; the right or posterior is narrow and pointed. In the fresh condition, or in

specimens which have been hardened *in situ*, the lips of the valve project as thick folds into the lumen of the caecum, and the opening may present the appearance of a slit or may be somewhat oval in shape. The circular and longitudinal muscle coats of the terminal part of the ileum are continued into the valve and form a sphincter. It must be added that direct observation of the living ileocaecal 'valve' does not corroborate this description (Rosenberg and DiDio 1969); in nine cases studied (through a caecostomy) the ileal projection was papillary in shape. Moreover, radiological evidence contradicts the concept of an effective valve at this junction.

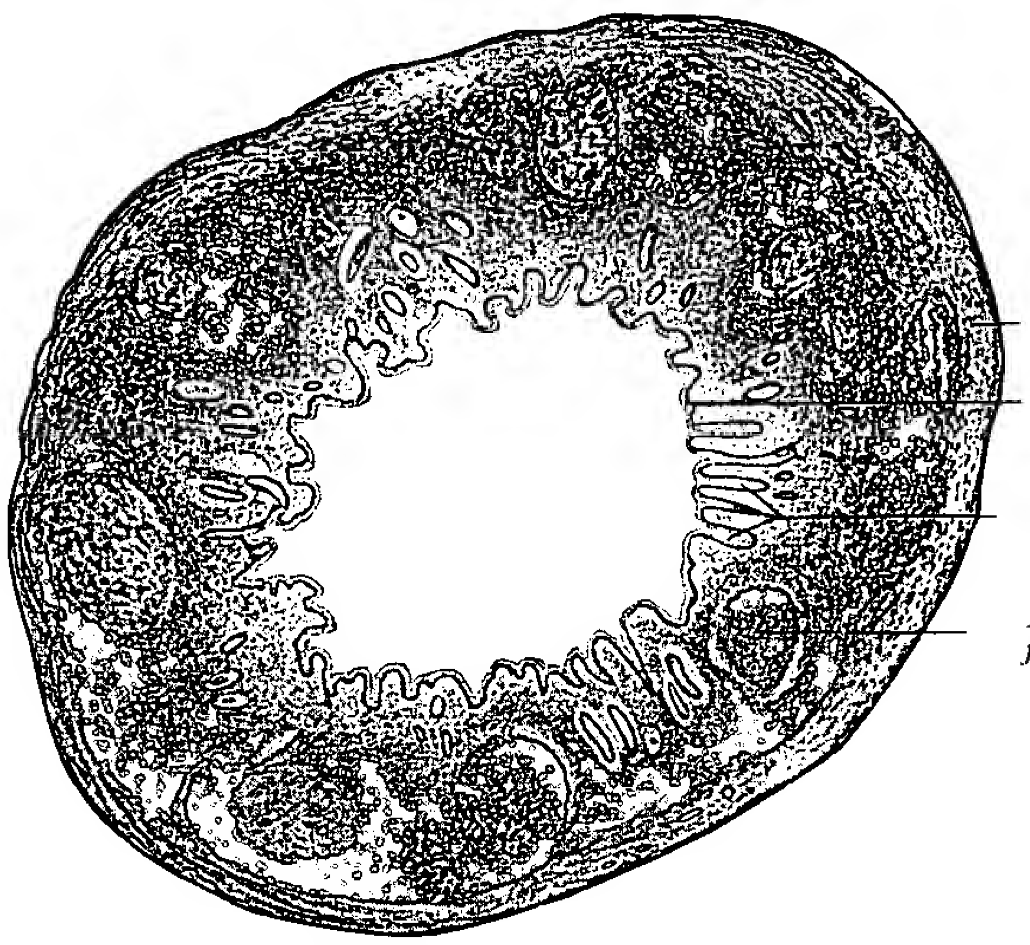
It may be added here that accumulations of circular fibres, sometimes described as sphincters, have been observed at various levels in all parts of the colon, and a large literature has developed on this topic (*see* DiDio and Anderson 1968; Rosenberg and DiDio 1969). The functional reality of most of these entities has not been established. It should be noted that all such sphincteric mechanisms must be balanced by an opposite, dilatatory activity.

The margin of the ileocaecal valve is formed by a reduplication of the mucous membrane and of the circular muscular fibres of the intestine. The longitudinal fibres are partly reduplicated as they extend into the valve (Jit and Singh 1956), though the more superficial longitudinal elements and the peritoneum are continued uninterruptedly from the small to the large intestine.

The surfaces of the valve directed towards the ileum are covered with villi and present the characteristic structure of the mucous membrane of the small intestine; while those turned towards the large intestine are destitute of villi and marked with the orifices of the numerous tubular glands peculiar to the mucous membrane of the large intestine. It is usually considered that the valve not only prevents reflux from the caecum into the ileum, but in all probability it also acts as a sphincter at the end of the ileum and prevents the contents of the ileum from passing too quickly into the caecum; the valve is kept in a condition of tonic contraction by impulses which reach it through the sympathetic nerves. The taking of food into the stomach initiates contraction of the duodenum and the rest of the small intestine, followed by the passage of ileal contents into the large intestine through the ileocaecal opening (the so-called gastro-ileal reflex).

THE VERMIFORM APPENDIX

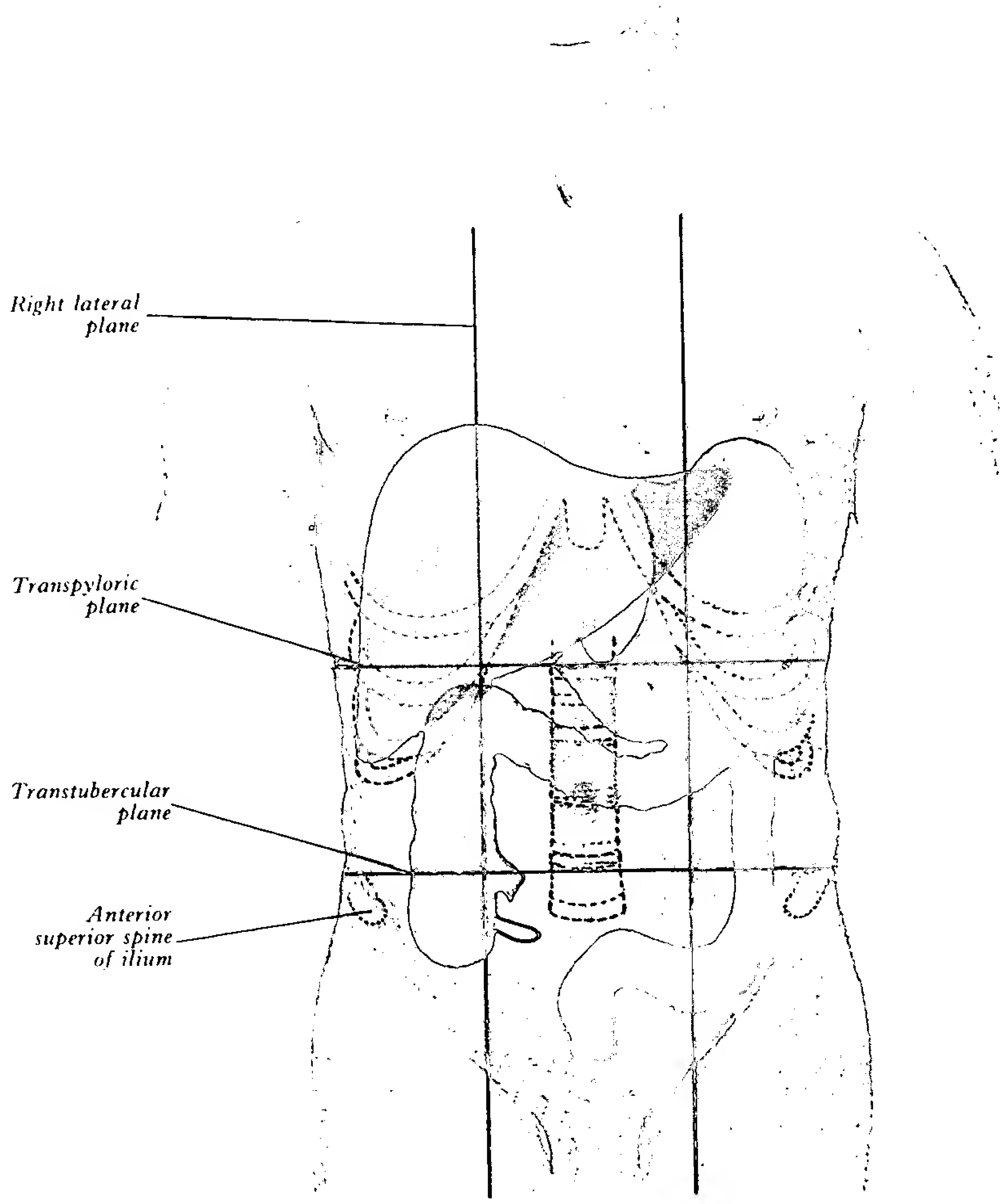
The vermiform appendix (**8**.121A, B) is a narrow, worm-shaped tube, which springs from the posteromedial wall of the caecum, 2 cm or less below the end of the ileum, and may occupy one of several positions: (*a*) it may lie behind the caecum and the lower part of the ascending colon (*retrocaecal and retrocolic*); (*b*) it may descend over the brim of the lesser pelvis (*pelvic* or *descending*), in which case it lies in close relation to the right uterine tube and ovary in the female; (*c*) it may lie below the caecum (*subcaecal*); (*d*) it may lie in front of the terminal part of the ileum and may then be in contact with the anterior abdominal wall; or (*e*) it may lie behind the terminal part of the ileum. In a study of 10,000 subjects (Wakeley 1933), the vermiform appendix was retrocaecal and retrocolic in 65·28 per cent, pelvic in 31·01 per cent, subcaecal in 2·26 per cent, pre-ileal in 1·0 per cent, and post-ileal in 0·4 per cent. Although these classical figures were based upon a very large series, subsequent literature, both anatomical and surgical, shows much contradiction. Buschard and Kjaeldgaard (1973), reporting upon a short series (234 autopsies), have compared the results of a number of studies (from 1885 to 1973), of which Wakeley's remains by far the largest. They classify all positions into two groups: *Anterior* (=pelvic and ileocaecal) and *Posterior* (retrocaecal and subcaecal). On this basis all but three of the eleven series quoted found the *anterior* positions more frequent. Like Wakeley these observers found *posterior* positions more commonly in their own Danish series, while in their German autopsies, the finding was reversed. Collins (1932) in the second largest series (4680), returned percentages which are the reverse of Wakeley's, the partition between anterior and posterior being 78·5 per cent and 21·5 per cent (Collins) and 32·4 per cent and 67·6 per cent (Wakeley). In view of these and other less contrasted disagreements, it is scarcely useful to continue to quote such figures. Perhaps the different observers involved have used different criteria in their examinations; perhaps, even, there are population divergencies. For the present, however, positional percentages for the vermiform appendix must be regarded as unreliable. The surface marking most used for the base of the appendix is the junction of the lateral and middle thirds of the line joining the right anterior superior iliac spine to the umbilicus (*McBurney's point*). (The latter is a useful surgical approximation, but as noted, considerable variation may occur). The three taeniae coli on the ascending colon and caecum converge on the base of the appendix, where they merge into its longitudinal muscular layer. The anterior taenia of the caecum is generally distinct and can be easily traced to the root of the appendix, thus affording a ready guide to it. The appendix varies from 2 to 20 cm in length, the average being about 9 cm. It is longer in the child than in the adult and may atrophy and become smaller after mid-adult life. It is connected by a short *mesoappendix* to the lower part of the mesentery of the ileum. This fold, in the majority of cases, is more or less triangular, and as a rule extends along the entire length of the tube. The main artery to the appendix, a branch of the lower division of the ileocolic artery (p. 716), runs behind the terminal part of the ileum and enters the mesoappendix a short distance from the base of the appendix. Here it gives off a recurrent branch which anastomoses at the base of the appendix with a branch of the posterior caecal artery, the anastomosis sometimes being of considerable size. The main appendicular artery runs towards the tip of the appendix, lying at first near to and afterwards in the free border of the mesoappendix. The terminal part of the artery, however, lies actually on the wall of the appendix and may become



8.122 A transverse section of human vermiform appendix. Magnification about $\times 20$.

thrombosed in inflammation of the appendix, which may result in gangrene or necrosis of its distal part. However, the arterial supply of the vermiform appendix may vary considerably. Numbers of accessory arteries are common; in 80 per cent of individuals there are two or more arteries of supply (Solanke 1968). The canal of the vermiform appendix is small, and communicates with the caecum by an orifice which is placed below and a little behind the ileocaecal opening. The orifice is sometimes guarded by a semilunar valve formed by a fold of mucous membrane. The lumen of the appendix may be partially or completely obliterated after mid-adult life. In view of its rich blood supply and histological differentiation, the vermiform appendix is probably more correctly regarded as a specialized than as a degenerate, vestigial structure. The configuration of the caecum and appendix in man and the anthropoid apes is probably less primitive than in the monkeys.

Structure. The layers of the vermiform appendix are the same as those of the intestine: serous, muscular, sub-mucous and mucous. The *serous* coat forms a complete investment for the tube, except along the narrow line of attachment of its mesentery.



8.123A Surface projection of the stomach, liver and colon. The outlines of the lumbar vertebral bodies, lower ribs, xiphoid process, and parts of the iliac crests are indicated.

Beneath it lies a layer of subserous areolar tissue. The *longitudinal muscular fibres* form a uniformly thick layer which invests the whole organ, except at one or two points where the longitudinal and circular layers may be both deficient, so that the peritoneal and submucous coats are contiguous over small areas. At the base of the appendix, the longitudinal muscle becomes thickened around the perimeter, to form incipient taeniae coli which becomes continuous with those of the caecum and colon. The *circular muscular fibres* form a thicker layer than the longitudinal fibres, and are separated from them by a small amount of connective tissue. The *submucous layer* is well developed, and contains a large number of masses of lymphoid tissue which cause the mucous membrane to bulge into the lumen and so render the latter of small size and irregular shape. The *mucous membrane* is covered by columnar epitheliocytes and attenuated antigen-transporting membrane or M cells (Owen and Nemanic 1978). Glands are few in number and penetrate deeply amongst the lymphoid tissue (8.122). In the normal human appendix the lymphoid tissue lies in the lamina propria and in the submucosa, where follicular and parafollicular zones can be distinguished; clusters of lymphocytes or immunoblasts also lie within or between surface epithelial cells where they possibly mature or differentiate into plasma cells (Gorgollón 1978). The lymphoid tissue of the lamina propria contains many plasma cells, together with lymphocytes, acidophilic leucocytes, mast cells and macrophages, all embedded in a fibrocellular reticulum. The submucosal follicles (germinal centres) contain immunoblasts, lymphocytes, macrophages, plasma cells and dendritic reticular cells, the last two being most abundant in the central regions of the follicles; cells similar to the dendritic reticular cells have been found in the human thymus (Kaiserling *et al.* 1974). The parafollicular zones are distinguished by aggregations of small lymphocytes, a scarcity of plasma cells, and by the presence of post-capillary venules lined by a tall endothelium through which lymphocytes may migrate. These endothelial cells have a surface coat of immunoglobulins which may be involved in the control of lymphocyte recirculation (Sordat *et al.* 1971). The *lymphoid masses* provide a local defence against infection, and have also been suggested as a possible homologue of the *bursa of Fabricius* in birds (p. 61) which is concerned with the acquisition of immunological competence by certain lymphocytes. Experimental evidence is, however, lacking. In many mammals, particularly herbivores, the caecum and associated appendix are large, and form an important site for the digestion of cellulose by symbiotic bacteria.

THE COLON

The colon may be considered in four parts—the ascending, transverse, descending and sigmoid.

The ascending colon, about 15 cm long, is narrower than the caecum. It begins at the caecum, and ascends to the inferior surface of the right lobe of the liver, where it is lodged in a shallow colic depression; here it bends abruptly forwards and to the left, forming the *right colic flexure* (8.111A). In surface projection it ascends to the right of the right lateral plane (8.123A), from the transtubercular plane to midway between the subcostal and transpyloric planes. It is surrounded by peritoneum except where

its posterior surface is connected by areolar tissue to the fascia over the iliacus, iliolumbar ligament, quadratus lumborum and the aponeurotic origin of the transversus abdominis, and to the perirenal fascia in front of the inferolateral part of the right kidney. The lateral cutaneous nerve of the thigh, usually the fourth lumbar artery and, sometimes, the ilio-inguinal and iliohypogastric nerves cross behind it. Sometimes it is almost completely invested with peritoneum, thus possessing a distinct but narrow mesocolon. In a series of 100, 52 per cent had neither an ascending nor a descending mesocolon, 14 per cent had both, 12 per cent an ascending, and 22 per cent a descending mesocolon (Treves 1885). It is in relation, anteriorly, with the convolutions of the ileum, the right edge of the greater omentum and the abdominal wall.

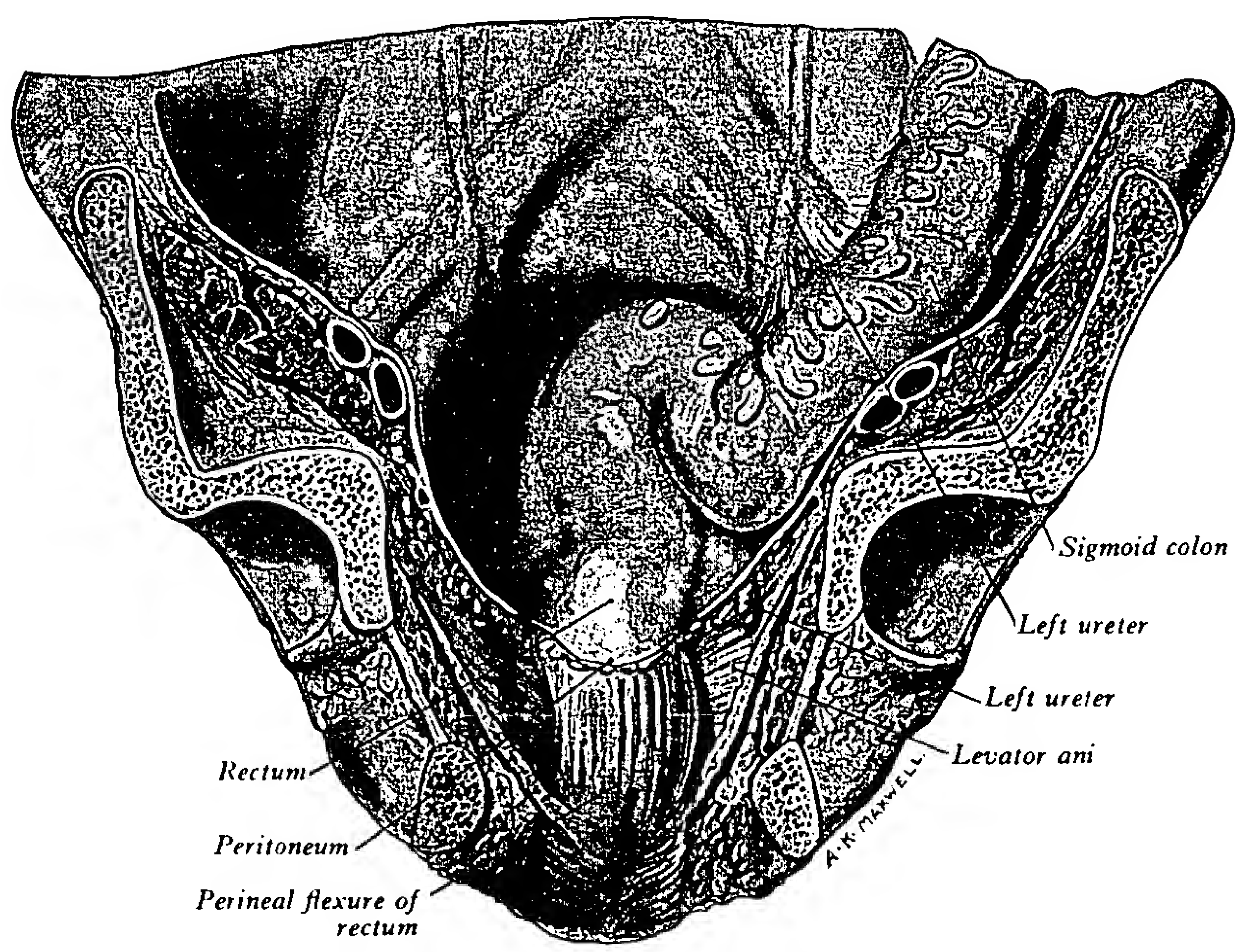
The right colic flexure comprises the terminal part of the ascending colon and the commencement of the transverse colon, which turns downwards, forwards and to the left. Behind, it is in relation with the lower and lateral part of the anterior surface of the right kidney. Above and anterolaterally, it is related to the right lobe of the liver; anteromedially, to the descending part of the duodenum and the fundus of the gall bladder. It is not covered by peritoneum on its posterior surface, so that this surface is in direct contact with the renal fascia. The flexure is not so acute as the left colic flexure.

The transverse colon (8.103), about 50 cm long, begins at the right colic flexure, placed in the right lumbar region, passes across the abdomen into the left hypochondriac region, and here curves sharply on itself, downwards and backwards, beneath the lateral end of the spleen, forming the *left colic flexure*. In its course across the abdomen it describes an arch, the concavity of which is usually directed backwards and upwards; towards its splenic end there is often an abrupt U-shaped curve which may descend lower than the main curve. Its surface projection (**8**.123) is drawn from a point, situated immediately lateral to the right lateral plane and midway between the subcostal and transpyloric planes, to the umbilicus, and then upwards and to the left to a point a little above and lateral to the intersection of the left lateral and transpyloric planes. The precise position occupied by the transverse colon is difficult to define, for it not only shows individual variation but its position varies in the same individual from time to time. Very commonly it lies in the lower umbilical or upper hypogastric region. It may be higher but frequently descends in a V-shaped manner, the apex of the V reaching well below the level of the iliac crests (*see* p. 1321). In a radiological assessment of the position of the transverse colon in the living (upright position), the level of the lowest part of the tube in 1,000 young adults varied greatly, even descending into the true pelvis. Moreover, the level varied as much as 17 cm in the same individual between the upright and recumbent positions (Moody 1927).

The posterior surface of its right extremity is devoid of peritoneum, and is attached by areolar tissue to the front of the descending part of the duodenum and the head of the pancreas. Between the head of the pancreas and the left colic flexure, the transverse colon is almost completely invested by peritoneum, and is connected to the anterior border of the body of pancreas by the *transverse mesocolon*. It is in relation, by its upper surface, with the liver and gall bladder, the greater curvature of the stomach, and the lateral end of the spleen; by its under surface, with the small intestine; by its anterior surface with the posterior layers of the greater omentum; its posterior surface is in relation with the descending part of the duodenum, the head of the pancreas, the upper end of the mesentery, the duodenojejunal flexure and some of the coils of the jejunum and ileum.

The left colic flexure (8.111) is the junction of the transverse and descending sections of the colon in the left hypochondriac region, and is in relation with the lower part of the spleen and the tail of the pancreas above, and with the anterior aspect of the left kidney medially; the flexure is so acute that the end of the transverse colon usually lies in contact with the front of the descending colon. The left colic flexure lies at a higher level than, and on a plane posterior to, the right colic flexure, and is attached to the diaphragm, opposite the tenth and eleventh ribs, by a peritoneal fold, named the *phrenicocolic ligament*, which lies below the lateral end of the spleen (p. 1330).

8.123B A radiograph of the abdomen after the administration of a barium enema which has filled the whole of the large intestine as far as the caecum and ileocaecal valve. (1) the caecum; (2) the right or hepatic flexure of the colon, which is much inferior to (3) the left or splenic flexure of the colon; (4) the sigmoid colon; and (5) the sacculations, or haustrations, which are clearly visible throughout most of the colon.

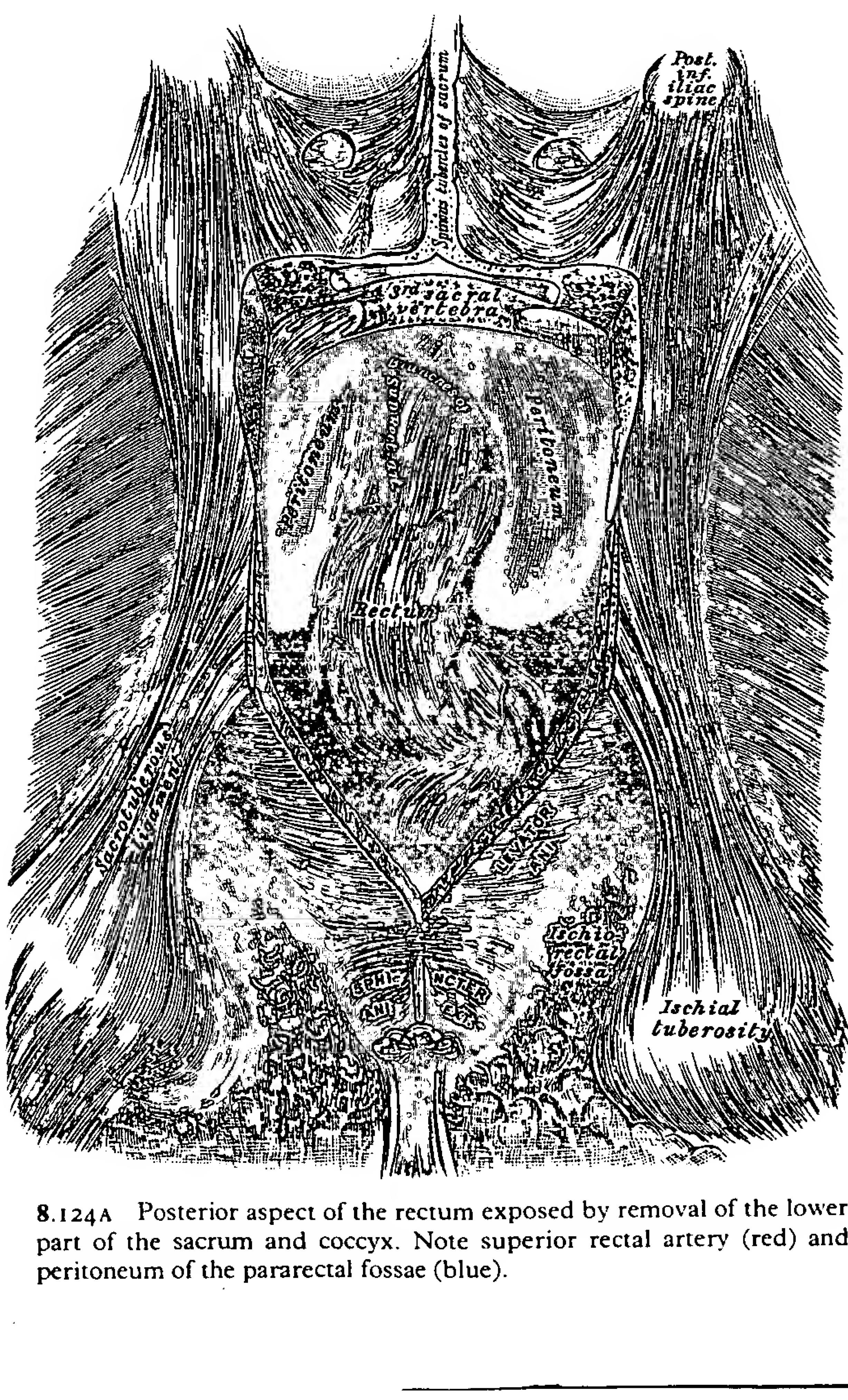


8.123C Oblique coronal section through the pelvis to expose the anterior aspect of the rectum.

The descending colon (**8**.111A), about 25cm long, passes downwards through the left hypochondriac and lumbar regions. At first it follows the lower part of the lateral border of the left kidney and then, at the lower pole of that organ, it descends, in the angle between psoas major and quadratus lumborum, to the crest of the ilium; it then curves downwards and medially in front of the iliacus and psoas major, and ends in the sigmoid colon at the inlet of the lesser pelvis. (The descending colon is sometimes described as ending at the level of the iliac crest, the part between that level and the inlet of the true pelvis being named the *iliac colon*.) In surface projection (**8**.123A) it passes downwards, just lateral to the left lateral plane, from a point situated a little above and to the left of the intersection of the transpyloric and left lateral planes, as far as the inguinal ligament. The peritoneum covers its anterior surface and sides, while its posterior surface is connected by areolar tissue with the fascia over the lower and lateral part of the left kidney, the aponeurotic origin of the transversus abdominis, the quadratus lumborum, the iliacus and the psoas major (**8**.111A). Numerous structures cross behind it. They include: the subcostal vessels and nerve, the iliohypogastric and ilio-inguinal nerves, the fourth lumbar artery (as a rule), the lateral femoral cutaneous, femoral and genitofemoral nerves, the testicular (or ovarian) vessels and the external iliac artery, all of the left side. The descending colon is smaller in calibre, more deeply placed, and more frequently covered with peritoneum on its posterior surface, than the ascending colon (p. 1355). Anteriorly it is related to coils of the jejunum, except in its lower part, which can be felt through the anterior abdominal wall when the abdominal muscles are relaxed.

The sigmoid colon (pelvic colon) (**8**.123C) begins at the inlet of the lesser pelvis, where it is continuous with the descending colon; it forms a loop which varies greatly in length, but averages about 40 cm, and normally lies within the lesser pelvis. The loop consists of three parts; the first part descends in contact with the left pelvic wall; the second crosses the pelvic cavity, between rectum and bladder in the male, and rectum and uterus in the female, and may come into contact with the right pelvic wall; the third arches backwards and reaches the median plane at the level of the third piece of the sacrum, where it bends downward and ends in the rectum. The sigmoid colon is closely surrounded by peritoneum, which forms a mesentery, the *sigmoid mesocolon* (p. 1330); this diminishes in length from the centre towards the ends of the loop, where it disappears, so that the loop is fixed at its junctions with the descending colon and rectum, but enjoys a considerable range of movement in its central region. Its relations are therefore subject to considerable variation. *Laterally* it is related to the external iliac vessels, the obturator nerve, the ovary (in the female), the ductus deferens (in the male) and the lateral pelvic wall. *Posteriorly* it is related to the internal iliac vessels, the ureter, the piriformis and the sacral plexus, all of the left side. *Inferiorly* it rests on the bladder, in the male, and on the uterus and bladder, in the female. *Above* and on its *right* side, it is in contact with the terminal coils of the ileum.

The position and shape of the sigmoid colon vary very much, and depend on (*a*) its length; (*b*) the length and freedom of its mesocolon; (*c*) the condition of distension; when distended it rises out of the lesser pelvis into the abdominal cavity, and when empty it sinks again into the pelvis; (*d*) the condition of the rectum and bladder (and the uterus, in the female); when these organs are distended the sigmoid colon tends to rise, and conversely. Racial variation in the size of the sigmoid colon has been noted (Lisowski 1969); in some groups—and particularly in Ethiopians—the incidence of a suprapelvic loop, which may be conducive to volvulus, is particularly high.

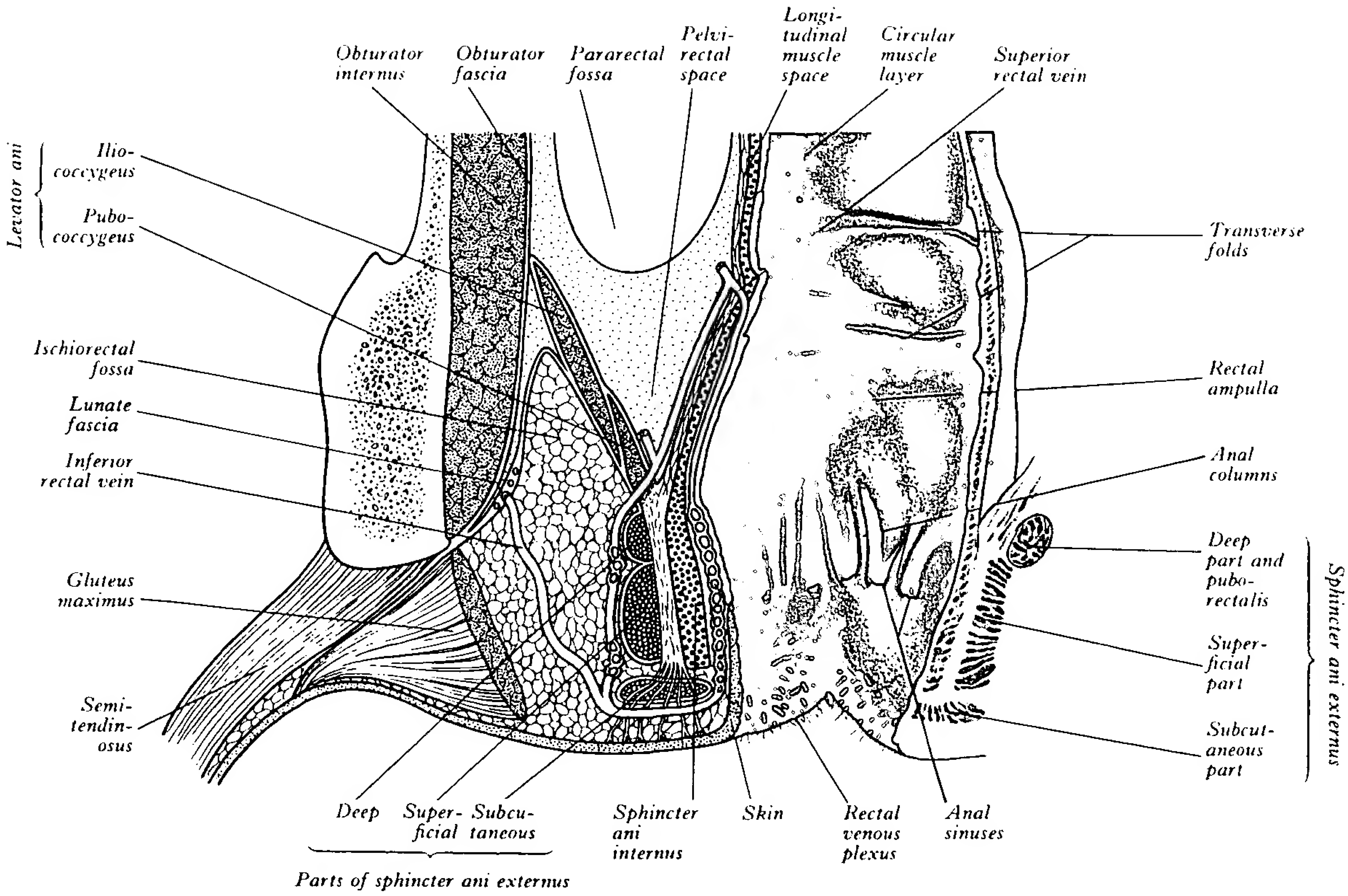


8.124A Posterior aspect of the rectum exposed by removal of the lower part of the sacrum and coccyx. Note superior rectal artery (red) and peritoneum of the pararectal fossae (blue).

THE RECTUM

The rectum (**8**.123C–124C) is continuous with the sigmoid colon at the level of the third sacral vertebra, the junction being indicated by the lower end of the sigmoid mesocolon. From its origin it descends, following the concavity of the sacrum and coccyx, forming an anteroposterior curve known as the *sacral flexure* of the rectum. It thus passes at first downwards and backwards, then downwards, and finally downwards and forwards to become continuous with the anal canal by passing through the pelvic diaphragm (p. 560). The *anorectal junction* is situated 2 to 3 cm in front of, and slightly below the tip of the coccyx; from this level, which in the male is opposite the apex of the prostate, the anal canal passes downwards and backwards from the lower end of the rectum, the backward bend of the gut at the anorectal junction being termed the *perineal flexure* of the rectum. In addition to its anteroposterior curve, the rectum deviates from the midline in the form of three lateral curves; the upper one is convex to the right, the middle one (which is the most prominent) bulges to the left, and the lower one is convex to the right; the beginning and end of the rectum are in the median plane (**8**.124A).

The rectum is about 12 cm long and its upper part has the same diameter as the sigmoid colon (about 4 cm in the empty state), but its lower part is dilated to form the *rectal ampulla*. The rectum differs from the sigmoid colon in that it has no sacculations, appendices epiploicae or mesentery, while the taeniae coli blend about 5 cm above the junction of the rectum and sigmoid colon to form two wide muscular bands which descend, one in the anterior and the other in the posterior wall of the rectum. The peritoneum is related only to the upper two-thirds of the rectum, covering at first its front and sides, but lower down its front only; from the latter it is reflected on to the bladder in the male, forming the rectovesical pouch of peritoneum, and on to the posterior wall of the vagina in the female, forming the recto-uterine pouch. The level of peritoneal reflexion is higher in the male, the rectovesical pouch being about 7·5 cm from the anus (the height to which the index finger inserted through the anus can reach); in the female the recto-uterine pouch is about 5·5 cm from the anus. In the male fetus the peritoneum extends on the front of the rectum as far as the lower end of the prostate (*see* p. 1420). On the sigmoid colon, the peritoneum is firmly attached to the muscle coat by fibrous

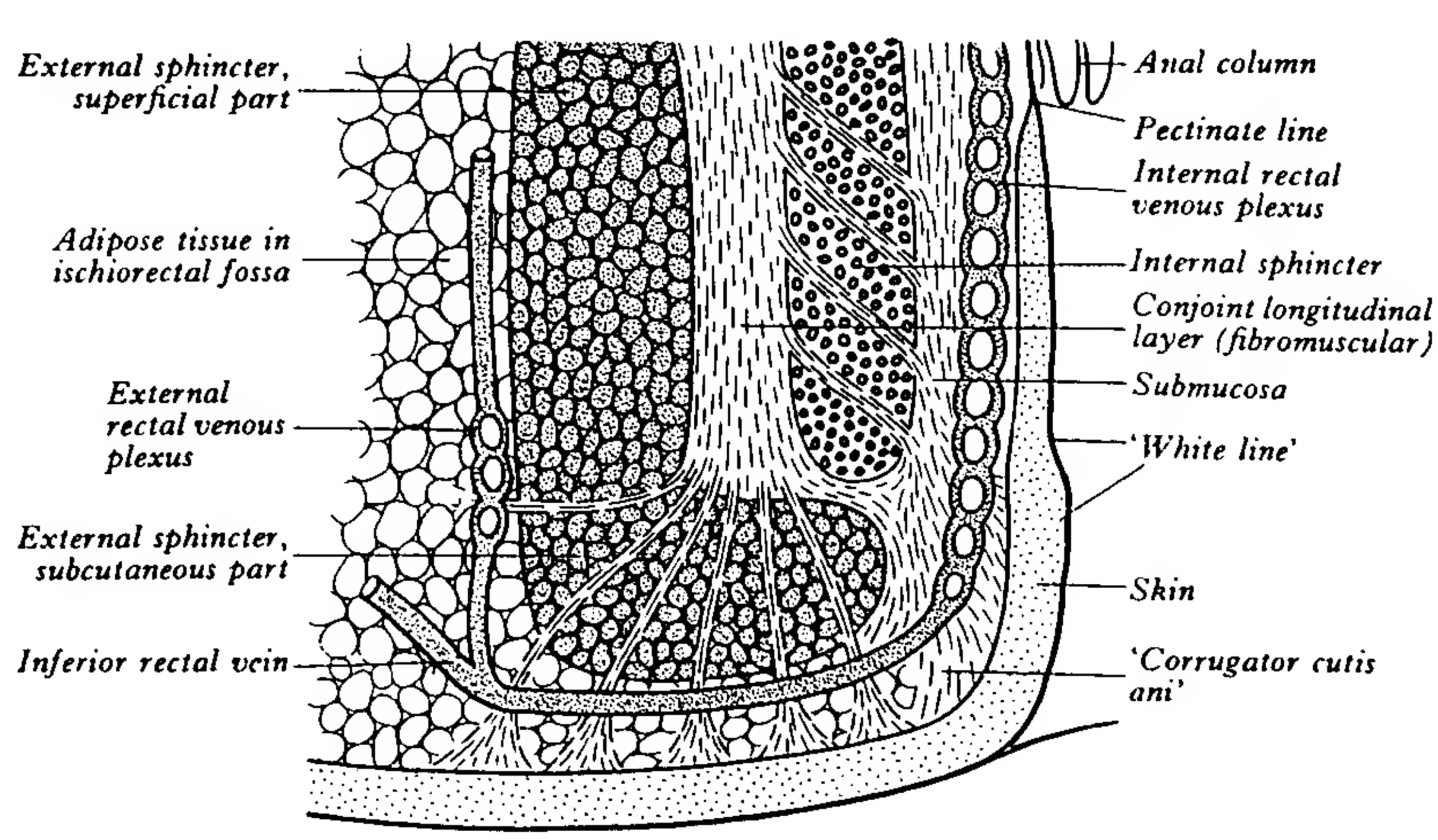


8.124B Diagram of a coronal section of the rectum and anal canal and the adjacent structures. (Adapted from Rauber-Kopsch, *Lehrbuch und Atlas der Anatomie des Menschen*, 1929.) The internal pudendal vessels, the dorsal nerve of the penis and the perineal nerve are shown transected in the lateral wall of the ischiorectal fossa, where they are traversing the 'lunate fascia' (pudendal canal).

connective tissue; but as it descends on the rectum, the peritoneum becomes more loosely attached to the muscle by fatty areolar tissue, thus allowing considerable expansion of this part of the gut.

In the empty state of the rectum, the mucous membrane of its lower part presents a number of longitudinal folds which are effaced by distension of the rectum. Besides these, there are permanent *transverse* or *horizontal folds* of a semilunar shape, which are most marked when the rectum is distended. Two forms of horizontal folds have been recognized (Jit 1961). One, consisting of mucous membrane, the circular muscle coat, and part of the longitudinal muscle coat, is marked on the outer surface of the rectum by an indentation. The other form is devoid of longitudinal muscle coat fibres, and bears no external surface marking. Commonly three folds are present, but their number is variable. The upper one is situated near the commencement of the rectum and may be on the left or the right side; occasionally it may encircle the gut and the lumen of the gut is then somewhat constricted at this site. The middle fold is the largest and most constant, and is situated immediately above the ampulla of the rectum; it projects from the anterior and right walls of the rectum just below the level at which the peritoneum is reflected from the anterior surface of the rectum; the circular muscle in this fold is more marked than in the others. The lowest fold is inconstant and lies on the left side, about 2·5 cm below the middle fold; sometimes a fourth fold is present on the left side, about 2·5 cm above the middle fold described above.

It has been suggested (Paterson 1912) that the rectum consists functionally of two parts, one above and the other below the middle fold, the upper part containing faeces and being free to distend towards the peritoneal cavity, while the lower part occupies a more confined situation, enclosed in a tube of



8.124C Part of 8.124B, enlarged to show greater detail.

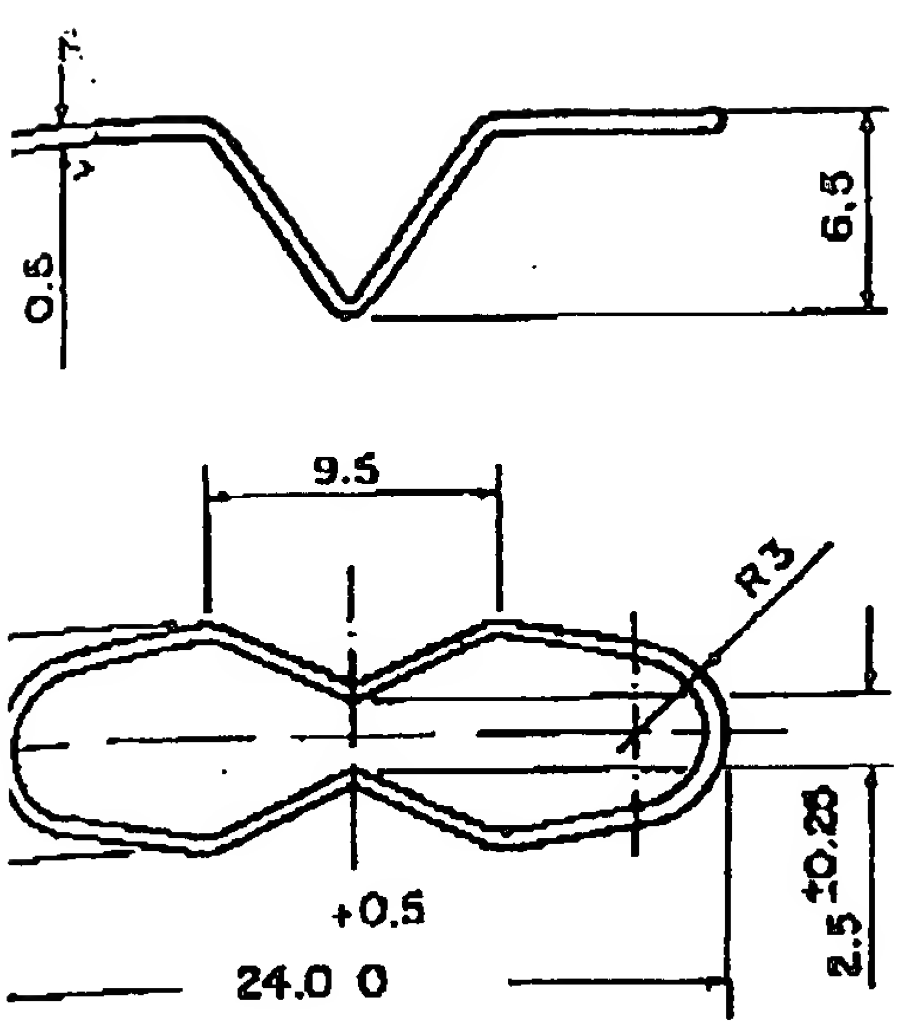


Fig. 2a. Tablet holder for the large cell.
(All measurements are expressed in mm unless noted otherwise.)

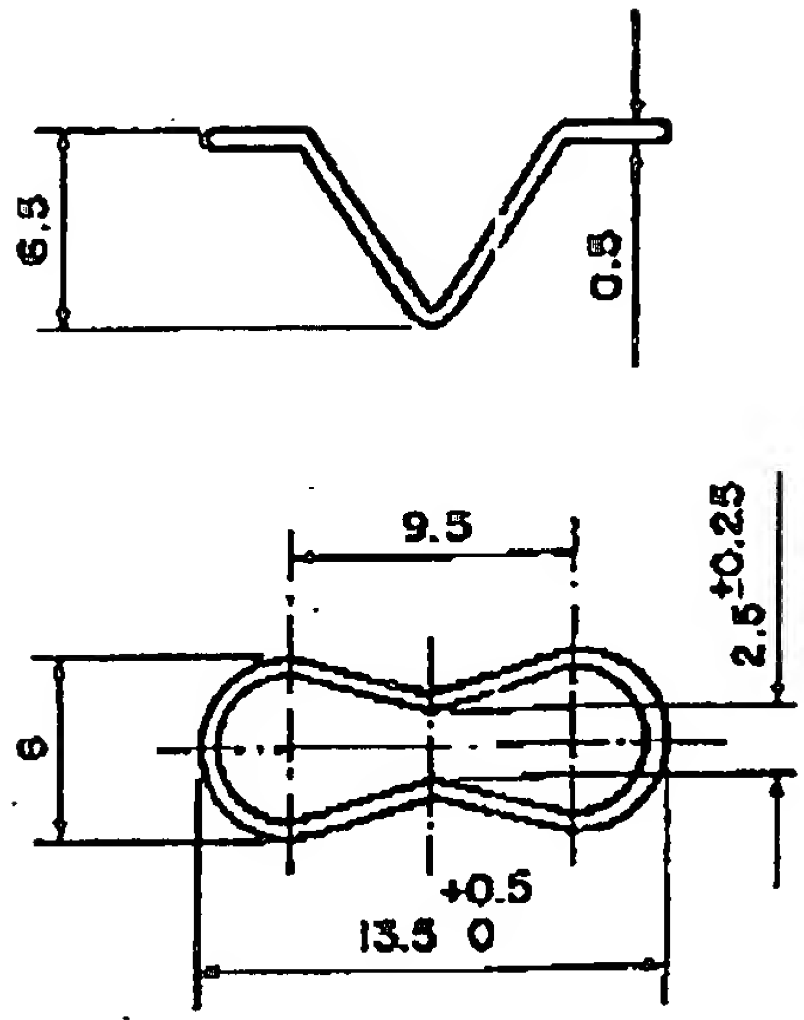


Fig. 3a. Tablet holder for the small cell.
(All measurements are expressed in mm unless noted otherwise.)

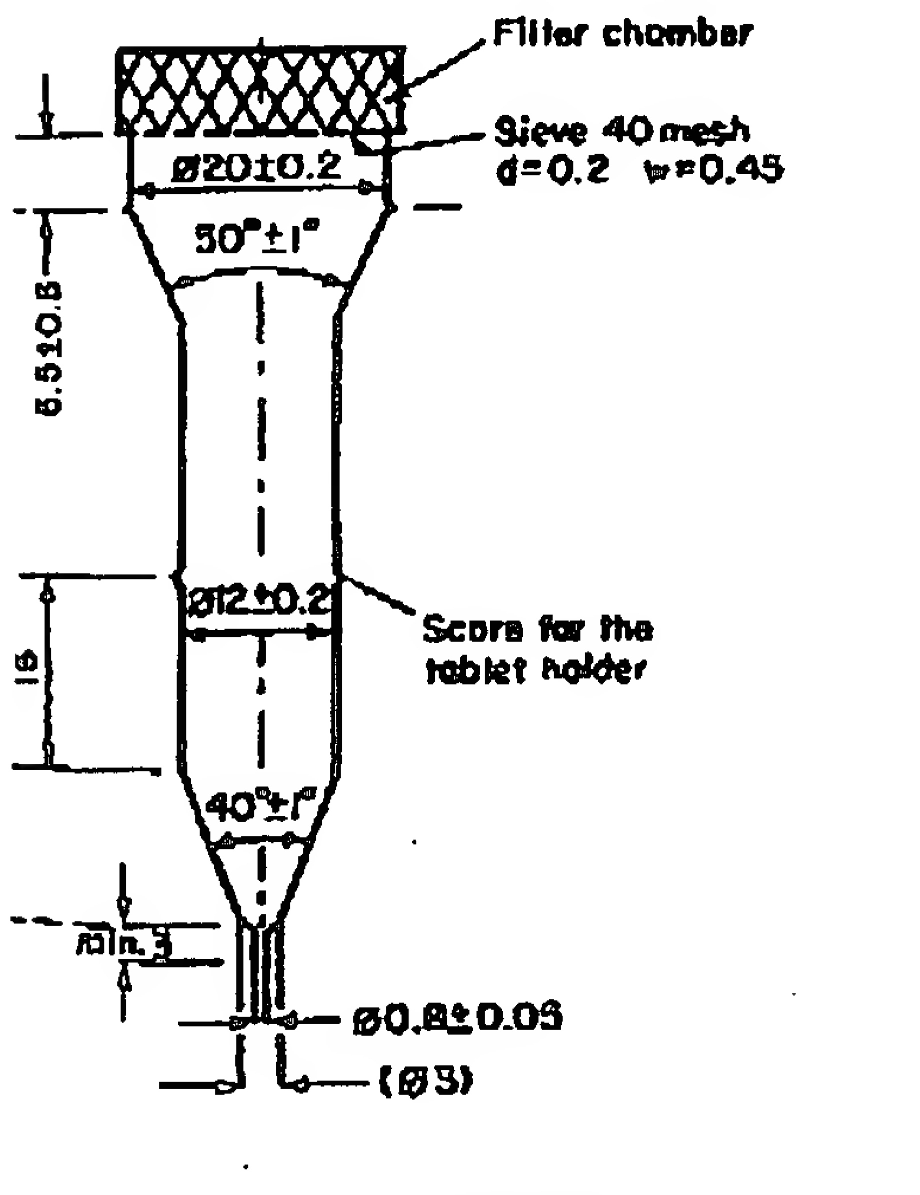


Fig. 3. Small cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

…t be on a level higher than the reservoir flasks. Tube… are as short as possible. Use polytef tubing with a …er diameter and chemically inert flanged-end con-…

…tem Suitability Test and Dissolution Medium—Proceed …ed under *Dissolution* ⟨711⟩.

Procedure—Place the glass beads into the cell specified in the monograph. Place 1 dosage-form unit on top of the beads or, if specified in the monograph, on a wire carrier. Assemble the filter head and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37 ± 0.5° through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time—The test-time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval.

Delayed-release (Enteric-coated) Articles—General Drug Release Standard

Use *Method A* or *Method B* and the apparatus specified in the individual monograph. Conduct the *Apparatus Suitability Test* as directed under *Dissolution* ⟨711⟩. All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A:

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 750 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

After 2 hours of operation in 0.1 *N* hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 2

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—[NOTE—Complete the operations of adding the buffer, and adjusting the pH within 5 minutes.] With the apparatus operating at the rate specified in the monograph, add to the fluid in the vessel 250 mL of 0.20 *M* tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 *N* hydrochloric acid or 2 *N* sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in *Acceptance Table 3* is 75% dissolved unless otherwise specified in the individual monograph. The quantity, Q, specified in the individual monograph, is the total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labeled content. The 5% and 15% values in *Acceptance Table 3* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 3

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than Q − 15%.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than Q − 15%, and no unit is less than Q − 25%.

Method B:

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 1000 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph. After 2 hours of operation in 0.1 *N* hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2* under *Method A*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Buffer Stage—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 *M* tribasic sodium phosphate [illegible] and adjusting, if necessary, with 2 *N* hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may be accomplished also by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.] Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Proceed as directed for *Interpretation* under *Method A*.

Transdermal Delivery Systems—General Drug Release Standards

Time—The test-time points, generally three, are expressed in terms of the labeled dosing interval, D, expressed in hours. Specimens are to be withdrawn within a tolerance of ±15 minutes or ±2% of the stated time, the tolerance that results in the narrowest time interval being selected.

DRUG DELIVERY TO THE GASTROINTESTINAL TRACT

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ELLIS HORWOOD LIMITED
Publishers Chichester

Halsted Press: a division of
JOHN WILEY & SONS
New York · Chichester · Brisbane · Toronto

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Relationship Between Pharmacokinetics and Gastrointestinal Transit

C G Wilson

Effective drug delivery via the oral route is principally modulated by two factors: physiological variables affecting the residence time in various regions of the gastrointestinal tract and the nature of the dosage form in which the drug is presented. For most drugs absorption is a passive process, the drug/plasma protein binding and hence removal of the free drug from the blood stream facilitating the diffusional drive. Nutrients are generally absorbed by active transport processes which are located in distinct areas of the gut, e.g. cyanocobalamin (vitamin B_{12}) uptake in the terminal ileum and the preferential absorption of fat soluble vitamins in the upper gastrointestinal tract. A few drugs demonstrate behaviour which is not compatible with simple partition theory, for example digitalis and other cardio-selective glycosides. Some penicillin derivatives, e.g. cyclacillin (1-aminocyclohexyl penicillin), also demonstrate carrier-mediated transport. The process is saturable, proceeds against an unfavourable concentration gradient, shows temperature dependence, and can be competitively inhibited by analogues such as amoxycillin. Drugs may also show regional differences in absorption which is dependent on pH and environment, particularly those compounds which have marked changes in solubility in the pH range experienced in the gut (pH 1.5 - 7.5). This effect is modulated by the presence of food which alters the pH, the viscosity and the transit time through various sections of the gut and a single clear effect may not be evident.

Controlled release technologies have been introduced as attempts to overcome some of the physiological and physicochemical limitations associated with drug delivery such as poor solubility or short biological half-life, but until recently progress was hampered by a lack of understanding of the behaviour of such systems *in vivo*. Techniques such as gamma scintigraphy have facilitated the study of the relationship between the transit of the formulation and drug absorption. The major limitation of this technique is that, in general, the drug itself cannot be labelled with a suitable radionuclide, since the gamma-emitting radionuclides of carbon, nitrogen and oxygen are positron emitters with half-lives too short to allow their use in monitoring of gastrointestinal transit. Despite this, gamma scintigraphy has revealed much concerning the relationship between drug release and absorption by use of radiolabelled compounds, the release of which *in vitro* and *in vivo* closely mimic the behaviour of the drug.

The time course of the pharmacodynamic response is a function of the pharmacokinetic properties of the drug which in turn may be influenced by formulation variables. Applications of modern controlled release technology have moved towards control of absorption via regulation of the input to the gastrointestinal tract. In pragmatic terms, the key features of therapeutic interest are the time for on set of drug action and the period over which effective drug levels are maintained. These parameters are strongly affected by transit through various regions of the gut and the manner in which diet and activity interacts with formulation variables is of great interest.

LAG TIME

An abrupt rise in plasma concentration usually occurs when a significant amount of drug arrives in the small intestine and thus is thought of as a consequence of the rate of gastric emptying of the formulation. However, oesophageal retention of capsules and tablets should be considered as a further influence on lag time particularly for single unit formulations.

In normal circumstances, the oesophageal transit of dose forms is extremely rapid, usually of the order of a few seconds. It is well recognised, however, that a tablet or capsule taken by a patient may lodge in the oesophagus, causing damage and irritation, particularly if the formulation is taken without water or the patient is in the supine position. Figure 1, taken from a recent study of oesophageal clearance of various formulations in man, shows the oesophageal transit of a capsule which lodged in the lower oesophagus (Wilson *et al.*, 1988). Lodging of the tablet or capsule formulation with a subject in the supine position occurred in at least 20%

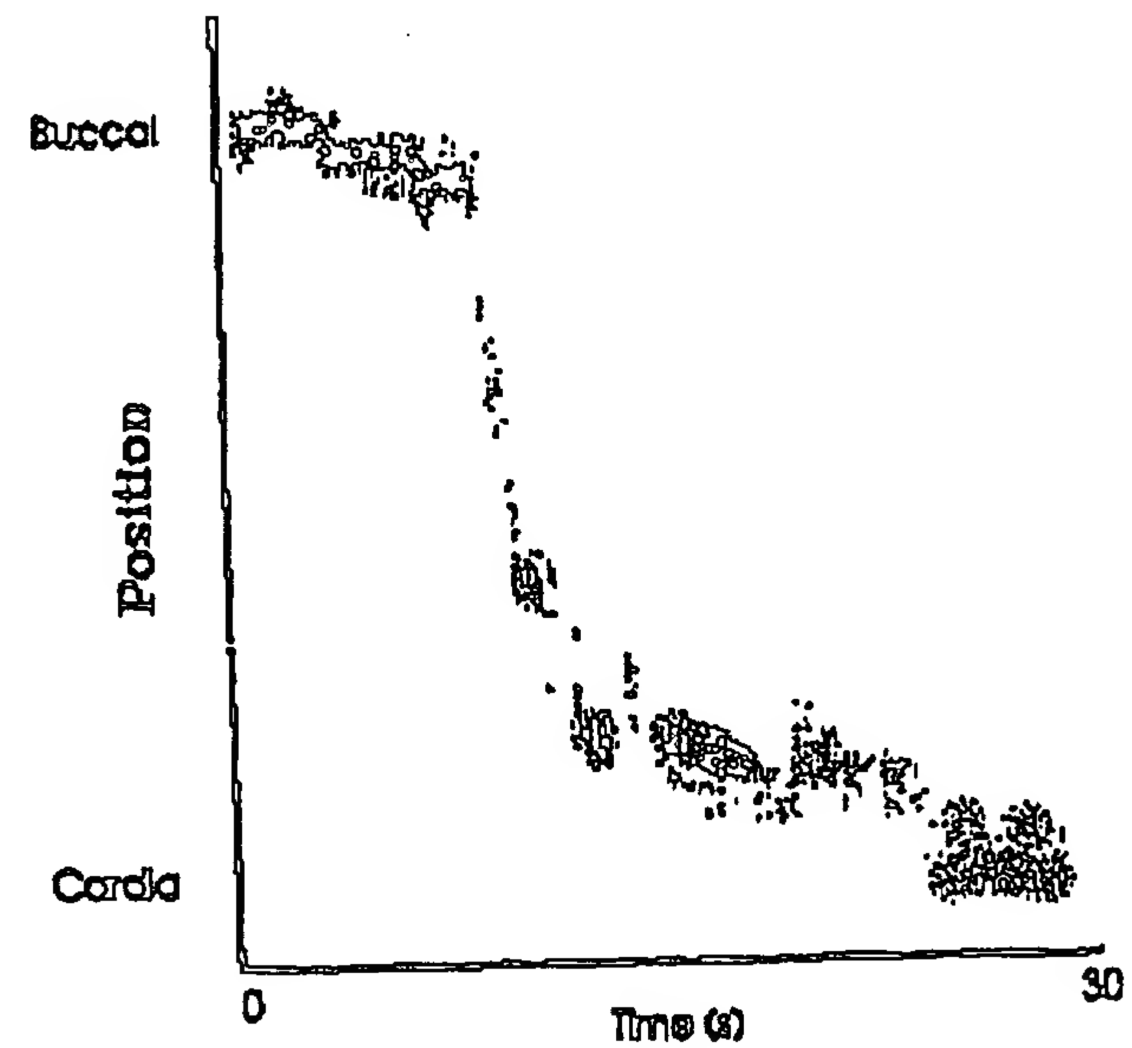


Figure 1 - Plot of oesophageal transit of a capsule. The unit lodged in the lower third of the oesophagus.

of investigated cases, and the unit, once it had adhered to the mucosa, was not be cleared by intake of water. This phenomenon may be dosage-form dependent. The interior surface of the oesophagus is moist rather than wet. A dosage form in contact with the mucosa will cause partial dehydration at the site of contact, as the unit hydrates, resulting in the formation of a gel between the formulation and the mucosa. The unit then disintegrates from its non-contact side. Disintegration is slow due to: the volume of dissolution fluid available being low (swallowed saliva) and a reduction in the surface area available for dissolution. The hydration of a sticky material against the mucosal epithelium greatly increases the changes for adhesion, which has been recognised as a hazard of formulations containing gelatin or cellulose derivatives.

Retention of tablets has been observed for prolonged periods after dosing resulting in a delay in the appearance of drug in the blood stream (Channer and Roberts, 1985). Diseases such as achalasia, in which transit is impaired by the inability of the lower oesophageal sphincter to relax, may increase the oesophageal residence and left side heart enlargement may exacerbate this problem.

GASTRIC EMPTYING

Very little absorption of drugs occurs from the stomach relative to the small intestine and therefore drug concentrations in the plasma are likely to be depressed until the gastric contents are delivered into the small intestine. Heading and coworkers (1973) completed a classic experiment in this field when they demonstrated that the rate of paracetamol absorption was related to the rate of gastric emptying. Large volumes of water (> 250 ml) given with formulations have two effects: first there is an increase in the fluid available for dissolution and secondly emptying of hypotonic solutions is rapid and a formulation may be carried through to the small intestine fortuitously.

Gastric emptying regulates the delivery of both food and co-administered drug into the small intestine; the differences in muscular tone between the pyloric antrum and the duodenum controlling the delivery to the small intestine. After the intake of food, the pylorus is closed down to permit the grinding and sieving mechanism of the antral mill. Early studies conducted in subjects who were fed with radiolabelled liver particles suggest that pieces greater than 2 mm in diameter are retained in the stomach until broken down into smaller fragments (Meyer *et al.*, 1981). The effective size in the dog is approximately 7 mm, since solid spheres of this size are retained (Meyer *et al.*, 1979). There is some controversy in the precise boundary size in humans as limited research carried out at Nottingham has suggested that tablets as large as 10 mm may pass through the pylorus with the chyme (Davis *et al.*, 1988a; Khosla *et al.*, 1988). It is feasible that the sieving behaviour of the pylorus may alter with different stages of both fed and fasted patterns of motility or with the nature of the meal ingested.

GASTRIC pH

It has been a general finding in normal volunteers that the basal pH before the intake of food is in the range 1.5 - 2.0, although some workers have found surprisingly high values for both dog and man. Kuna (1964) determined that in 403 tests in dogs, 77% had a gastric pH of 5 or above compared with a frequency of 35% in 1556 studies in man. Changes in pH caused by food are easily noted using indwelling probes or radiotelemetry capsules and a marked rise to pH 4 is usually evident, particularly if the meal contains a large amount of easily digested protein (Figure 2). Hardy *et al.* (1987) noted that in one of the subjects taking part in an evaluation of an enteric coated naproxen product, the pH rose to a transient peak of 6.5 when

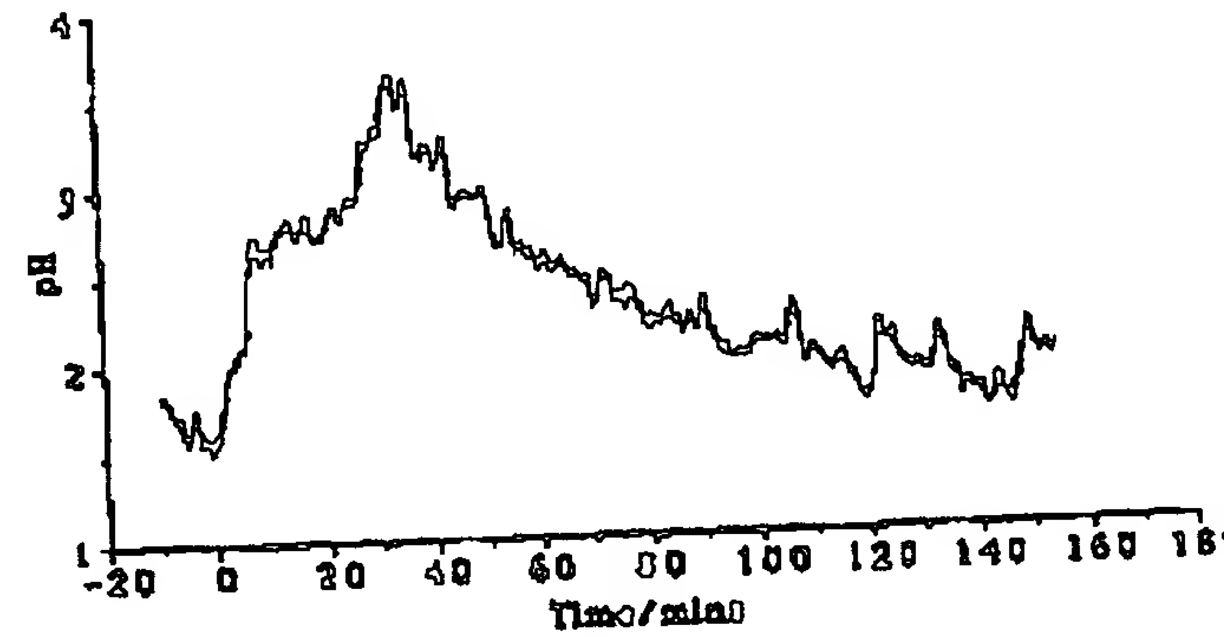


Figure 2 - Mean pH profile in the stomach after a test meal. (Mean, n = 6)

the subject consumed lunch. This may be sufficient to cause a significant increase in the rate of dissolution of an enteric coating, particularly for a pelleted or microparticulate system. On passing from the proximal to the distal duodenum there is a sharp rise in pH, from about 3 to 6 (Ovesen *et al.*, 1986).

EFFECT OF FOOD ON DRUG ABSORPTION

The ingested food provides a large volume in which a formulation will be dispersed. The viscosity and pH alterations produced by food can markedly alter the rate of disintegration of dosage forms as has been shown in the study described by Casey and coworkers (1984). Using scintigraphic techniques, the *in vivo* dispersion and gastric emptying of glibenclamide dosed in a hardened gelatin liquid fill product was studied in man. In the fasting state, the beginning of drug absorption, indicated by the first appearance of the drug in the plasma, correlated well with the start of in vivo disintegration. Food markedly affected the dispersion of the dosage form (assessed by visual inspection of the images) and delayed the appearance of the drug in the plasma by an hour, which correlated with the lag time before gastric emptying began.

The time of dosing with respect to intake of food is also important as shown in recent studies, in which the gastric emptying of labelled pellets contained within hard gelatin capsules were dosed 10 minutes prior to a meal, midway through a meal or 10 minutes after a meal. The effect of pre-

isparsing pellets, (analogous to theophylline 'Sprinkle' systems) was also investigated (O'Reilly *et al.*, 1987). The particles were released from all capsules within a few minutes. After dosing in the capsule during or after meal, the pellets tended to remain in the upper half of the stomach. In these cases, the gastric emptying pattern was approximately linear with time. The gastric emptying half-times of between 3-4 hours were similar in all the experiments; however, over the initial 100 minutes, the particles from the capsules taken immediately before the meal emptied fastest and the emptying exhibited an exponential pattern with time. For the pre-dispersed pellets, the distribution in the stomach was more uniform, although the gastric emptying rates were similar for pre-dispersed pellets or pellets from capsules given midway through the meal.

For highly water soluble drugs, dissolution in the residual gastric contents of a fasting subject (approximately 50 ml) is not rate limiting and the delivery of drug into the small intestine is the rate-determining step in absorption. However, for poorly soluble drugs prolonged gastric residence may provide more time for drug dissolution and this effect has been the ascribed cause of the increased blood levels observed when such a drug is taken with food. Acyclovir shows a bell-shaped pH-solubility profile and is most soluble above pH 10 and below pH 2.2. At a pH of 1.0 the solubility is 12 mg ml^{-1} but for the pH conditions likely to be encountered in the mid and distal small intestine, the maximum solubility is estimated to be 1-2 mg ml^{-1}. Lewis and coworkers (1986) have shown that acyclovir absorption was increased when the contact time of the drug was prolonged by the subject sipping solution over a 4 hour period. However, other studies on the effects of light and heavy breakfasts on the absorption of a dose of 400 mg acyclovir suspension showed that the heavier meal significantly decreased the bioavailability even though the rate of gastric emptying was slowed and small intestinal transit time was prolonged by the heavier meal (Wilson *et al.*, 1987). It was suggested that the heavier meal caused a greater dilution of the suspension and elevated gastric pH for a longer period decreasing the absorption of the drug.

There are instances in which a drug has shown both increased and decreased absorption when taken with food and this appears to be due to a formulation variable. Serum theophylline levels were doubled when an 800 mg dose of 'Uniphyl', a cellulose acetate matrix formulation with pH independent *in vitro* dissolution, was taken with a high fat breakfast when compared with fasting levels (Karim, 1988). Similar results were obtained by Lagas and Jonkman (1983) with 'Theograd' tablets (porous matrix controlled release tablets with pH independent *in vitro* dissolution). Pellet formulations which are pH dependent such as 'Theo-24', also show increased absorption in the presence of a high fat meal. The magnitude of the effect can be so large that food induced dose dumping of the drug is considered to be a hazard in once a day therapy (Vaughan *et al.*, 1984). Conversely, 'Theo-Dur Sprinkle' (pellet formulation with pH independent *in vitro* dissolution) showed a marked reduction in absorption when given with a high fat meal when compared to the fasted state. When the 'Theo-24' preparation was given 1 hour prior to a high fat breakfast the peak levels were reduced compared to when it was given immediately before the breakfast (Karim *et al.*, 1985). Inspection of the data showed that there is no clear factor which emerges other than that the formulation with the fastest rate of release shows a decrease in absorption with intake of fat, whereas the formulation with the slowest release shows an increase in absorption when given with fat.

Sournac and coworkers (1988) have shown a close correlation between the *in vitro* rates of release of $^{99}Tc^{m}$-labelled diethylenetriaminepentaacetic acid ($^{99}Tc^{m}$-DTPA) and theophylline from a controlled release tablet. The tracer was adsorbed onto lactose and incorporated into a hydrophilic matrix tablet consisting of 300 mg of drug plus hydroxymethyl cellulose, lactose, silicon dioxide and magnesium stearate as excipients. The marker was then used to examine properties of release of the tablet. The data showed that release of theophylline would be essentially complete by the time that the tablet reached the caecum (90% released over six hours).

CONTACT OF MATERIALS WITH THE SMALL INTESTINE

The rate of gastric emptying of the components of a meal differ, which may have an important consequence for drug absorption, since released drug disperses in the food mass and is adsorbed onto the components of the meal. Liquids are generally considered to empty as a first order process at a rate proportional to the square root of the volume (Hunt and MacDonald, 1954), whereas solids empty more linearly with time. The rate of gastric emptying and intestinal transit of many diverse pharmaceutical forms has been measured in the large number of scintigraphic studies carried out by the research group at Nottingham. The results obtained have been summarized by Davis *et al.* (1986) and have shown that transit of the dosage form through the small intestine is largely independent of food intake or formulation effects.

Food may modulate the time of exposure of drug to the absorbing surfaces of the small intestine by virtue of the effects of energy content of the meal, since food is emptied into the duodenum at an isocalorific rate. Thus, a large meal empties slowly and whilst food remains in the stomach, slowly-disintegrating formulations such as those consisting of drug in a non-disintegrating matrix are retained. The released drug may percolate out

of the stomach in the chyme, over a prolonged period until the stomach is empty. The "housekeeper" activity is then initiated which removes undigested debris by contractions against an open pylorus and strong peristaltic waves push the remaining material into the intestine.

Food components do not empty uniformly and Malagelada and co-workers (1984) have shown that the gastric emptying rates of $^{99}Tc^{m}$-DTPA solution and ^{131}I-labelled fibre are extremely different. Although large particles are retained, ^{131}I-labelled fibre strands (1-3 mm long, which are thin and pliable) stay intact and are able to leave the stomach during feeding, though at a slower rate than liquids. The transit of these fibres in the small bowel reflects the behaviour of a particular class of solids, i.e. those that retain their solid character in the intestine. Such particulate matter in the chyme spreads over a considerable length of the small bowel during feeding, due to the combination of slow emptying from the stomach and the gradual slowing of transit as material approaches the ileocaecal junction.

Comparison of the small intestinal times of ^{131}I-fibre and $^{99}Tc^{m}$-DTPA suggests that water soluble substances and particulate matter in chyme travel at the same speed along the small bowel during feeding. They do not move concurrently, however, as the bulk of the water soluble tracer 99Tcm-DTPA precedes the bulk of the ^{131}I-labelled fibre, which empties more slowly from the stomach than the liquid phase. The solid phase, though moving at a similar speed, therefore reaches the colon more slowly than the liquid phase, thus the time difference is determined by the stomach rather than the small intestine.

Kaus *et al.* (1984), using a three dimensional display technique to estimate the intestinal transit of a small perspex capsule, found that transit through the duodenum was so rapid that it could not be measured, but thereafter the capsule moved through the small intestine with a mean transit rate of between 4.2 and 5.6 cm per minute. It is interesting to speculate why transit through potentially the most absorptive region of the gut is so rapid; presumably this is a function of the duodenum's role in sampling the gastric contents to modulate gastric emptying by regulation of the difference in pyloric antrum-duodenal bulb pressure.

One of the most interesting applications of gamma scintigraphy is to examine the relationship between pharmacokinetics and gastrointestinal transit. The small number of teams working in this field has meant that progress has been slow. The technique has much potential as may be illustrated in recent studies on non-steroidal anti-inflammatory drug (NSAID) formulations. Once a day therapy with these drugs, as with others, is perceived as a therapeutic advantage and a large number of sustained release formulations have appeared on the market. A typical example is the sustained release acetylsalicylic acid formulation, 'Zorprin' (Boots Pharmaceutical, USA), in which the aspirin (800 mg) is formulated with

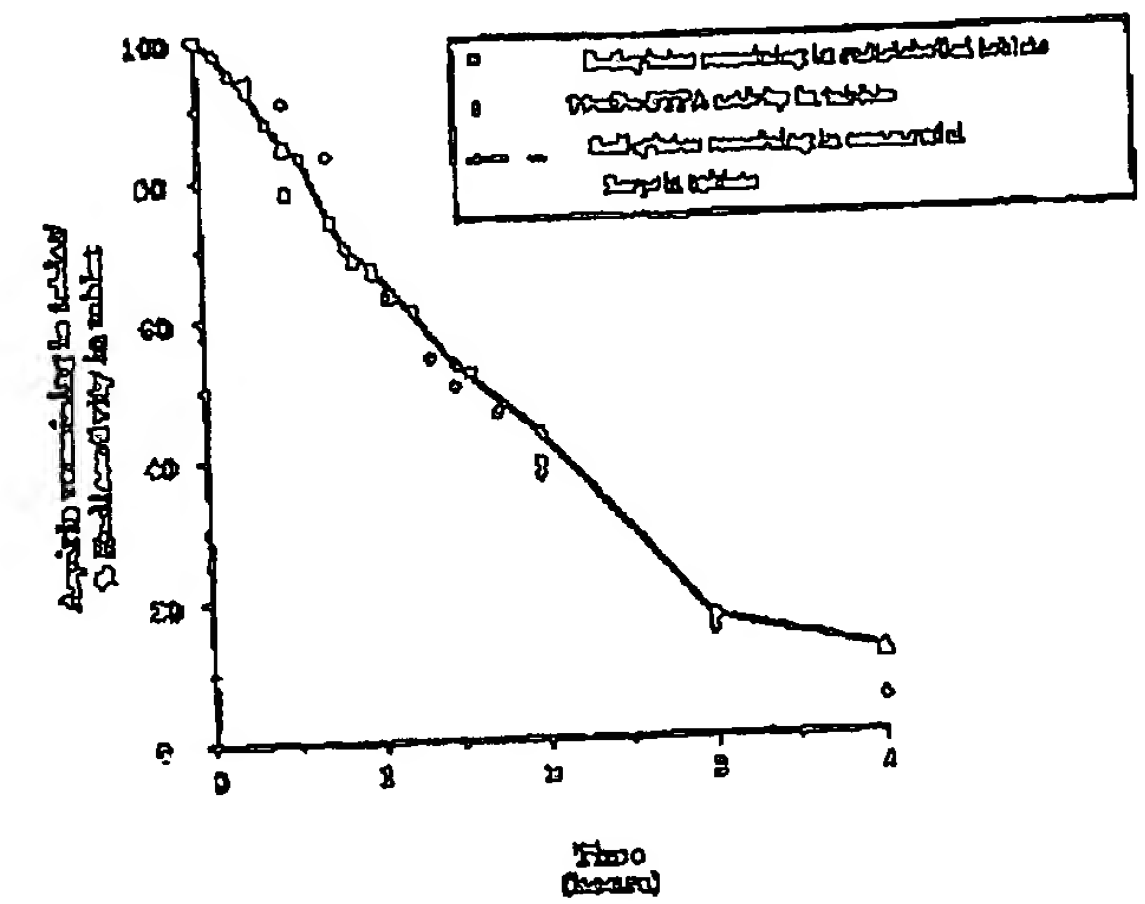


Figure 3 - Release of marker ($^{99}Tc^{m}$-DTPA) and salicylates from a radiolabelled sustained release acetylsalicylate product (from Wilson *et al.*, 1984).

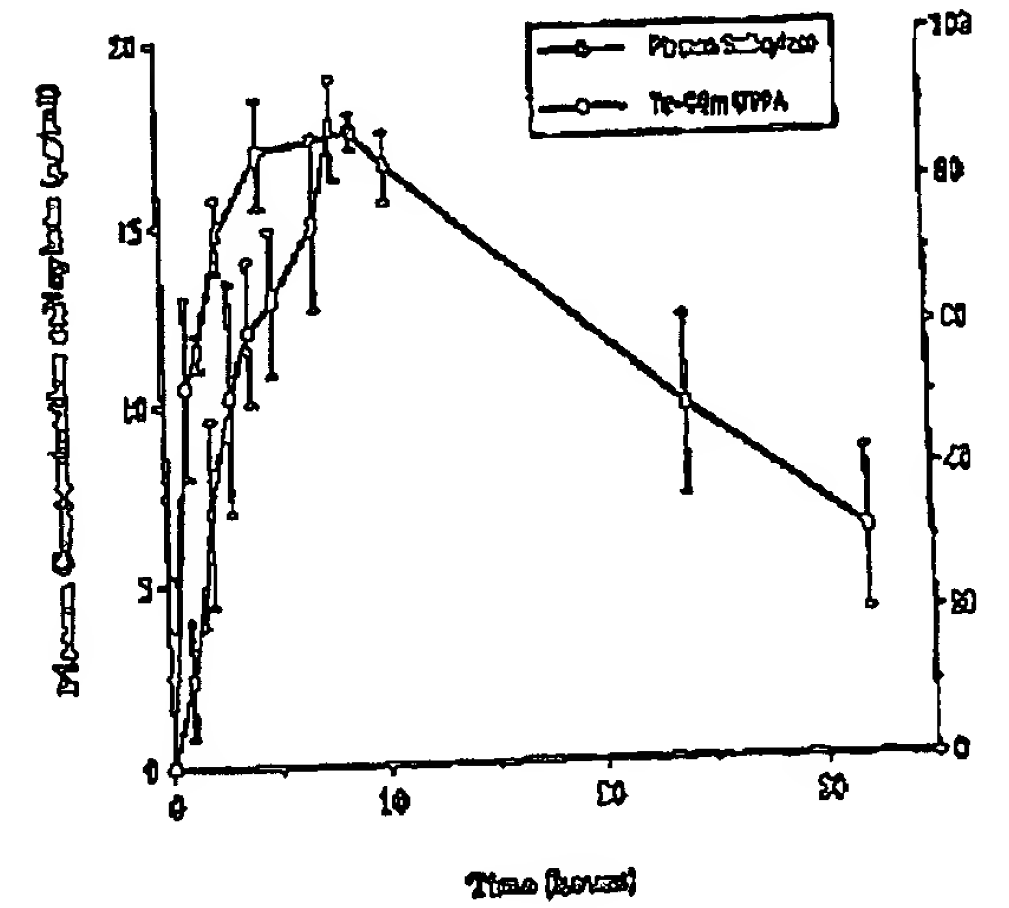


Figure 4 - Relationship between disintegration of matrix and plasma salicylate levels for a sustained release acetylsalicylate product (from Wilson et al., 1984)

ellulose acetate phthalate (10 mg). Scintigraphic studies have been used o examine the rate of dissolution of the formulation by incorporation of ^{99}Tc^{m}-DTPA into the tablets and administering them to fasted volunteers Wilson *et al.*, 1984). The *in vitro* release rates of ^{99}Tc^{m}-DTPA and alicylates were found to correlate closely using USP method 2 (Figure 3). Tracer was released from the matrix in pseudo-zero order fashion and ermination of drug release correlated with the inflection point in the plasma curve when excretion was faster than absorption (Figure 4).

In recent studies, double peaks have been noted in the plasma concentration time profiles for the NSAID drugs ibuprofen and ketoprofen given in sustained release formulations, particularly in fasted individuals. Parr and coworkers (1987) described a scintigraphic assessment of a sustained release ibuprofen tablet which was radiolabelled by incorporation of ^{170}Er-erbium oxide (2 mg). The tablets were irradiated by a neutron source to convert the non-radioactive erbium oxide to 171Er-erbium oxide which is a gamma emitter having a half-life of 7.5 h and an energy suitable for imaging with a gamma camera. The tablets were administered to eight fasted volunteers and the transit and dissolution of the tablets followed by gamma scintigraphy. Several of the subjects in the study were observed to have two peaks in their ibuprofen-serum concentration time curves and the authors commented that this phenomenon had been observed previously in standard pharmacokinetic studies. Since the drug does not undergo enterohepatic recirculation, the double peak was postulated by the authors to be produced by the loss of integrity of the dosage form in the large bowel.

A secondary peak in the plasma concentration profile could be utilised to provide a boost to concentration in the target tissue and it would be extremely useful to capitalise on this phenomenon to improve NSAID therapy. Shah (1988) has described a bimodal release pattern from drug-polymer matrix tablets particularly those containing cellulose ethers. He argued that zero-order release may not be totally appropriate for optimising drug delivery since transport across the epithelia in the stomach and large bowel would be slower than in the small intestine due to the smaller surface area. He proposed that the bimodal system, characterised by high initial release followed by slow constant release and a final faster release may compensate for physiological limitations. Pragmatically it would be extremely difficult to obtain this release profile due to the unpredictable effects caused by time of dosing relative to food intake. Figure 5 compares the effect of the fasted and the fed state on the mean plasma-ibuprofen concentration time profile (Wilson *et al.*, 1989) and Figure 7 shows the rate of disintegration of the matrix. Although food did not significantly alter the rate of release of drug from the formulation (Figure 6), the bimodal peaks are much less evident in the fed compared to the fasted state and the slower

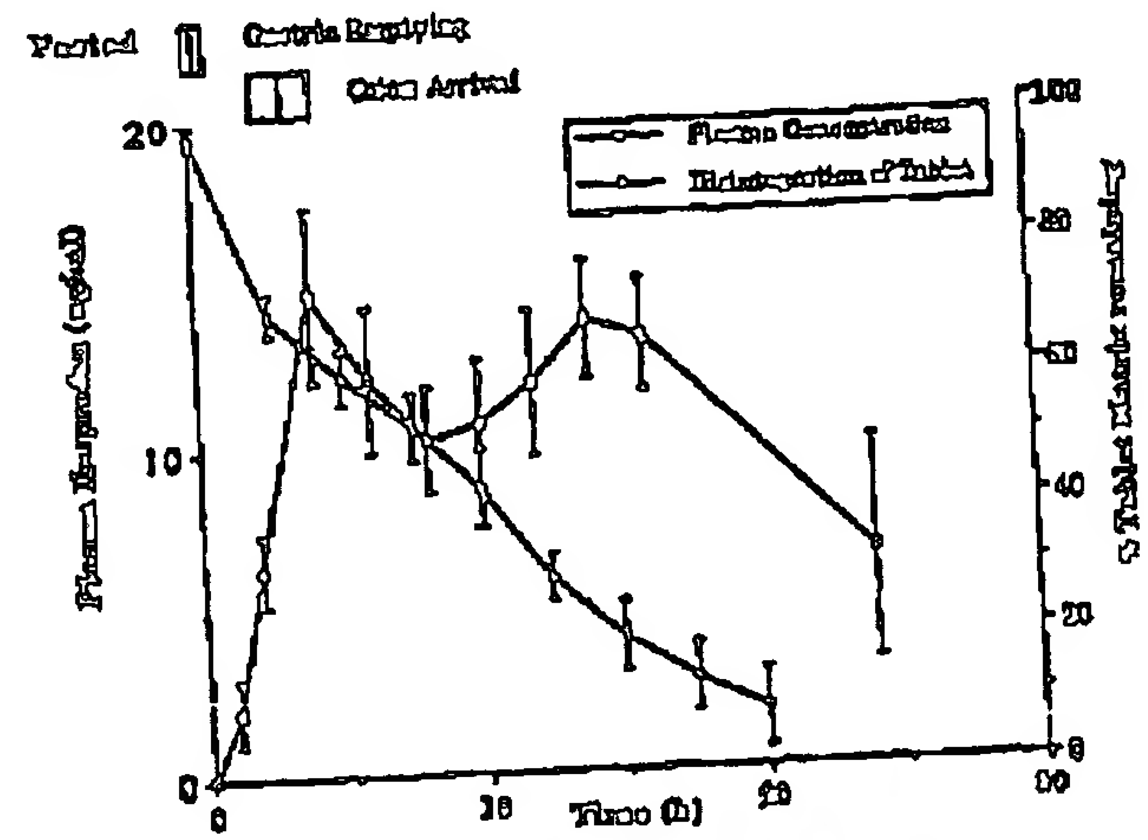
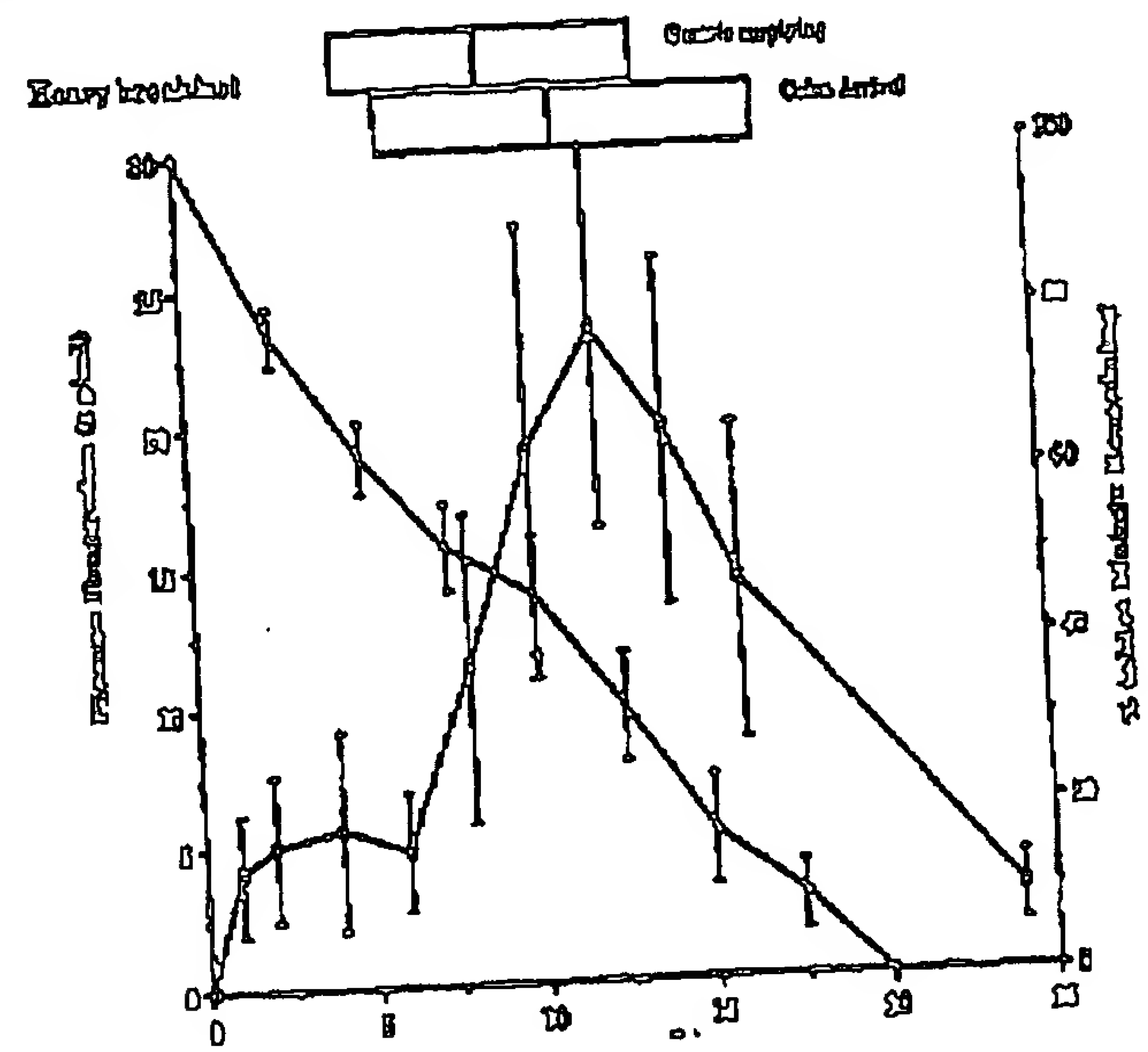


Figure 5 & 6. Effect of food on the plasma concentration - time profiles following administration of a sustained-release ibuprofen tablet to fasted volunteers (above) and fed volunteers (below). Boxes plot indicate mean gastric emptying / colon arrival ±1 SD (from Wilson *et al.*, 1989)



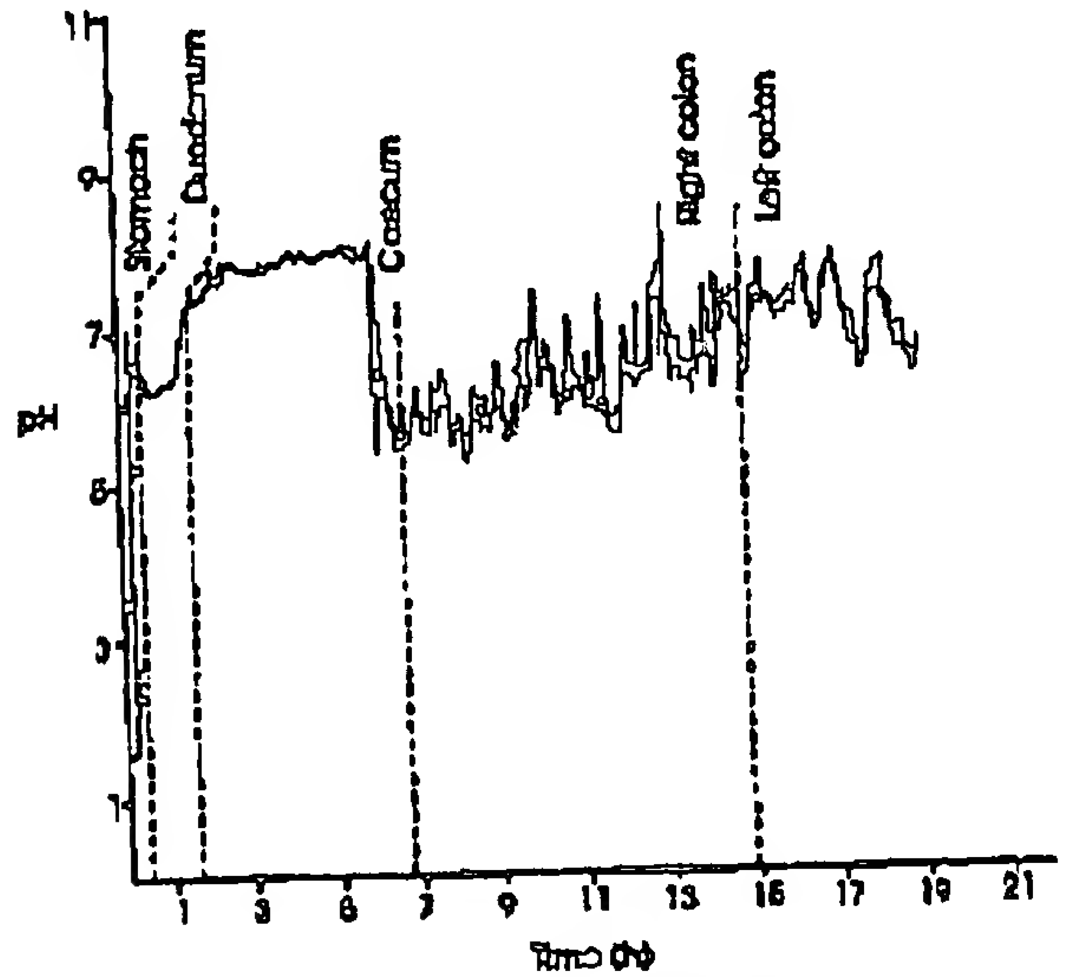


Figure 7 - pH profile throughout the gastrointestinal tract.

for long periods results in a delayed peak concentration. The scintigraphic assessment showed that the formulation disintegrated at the hepatic flexure of the colon. As the formulation enters the colon it is subjected to an abrupt fall in pH to around pH 5.5 - 6 (Figure 7). There is a sharp decrease in solubility of the drug around the pKa (about 5.5) and therefore in the caecum dissolution would be decreased. At the hepatic flexure, the pH rises to above 7 and dissolution would be expected to be faster which would result in a bimodal peak, particularly in the fasting and lightly fed states. Where a large meal is given, the food would provide an absorbing secondary release surface which would hide the modulations produced by caecal pH. This was the point at which the formulations disintegrated. There was not, however, an exact correlation between the time of disintegration and the peak plasma concentration.

Oberle and Amidon (1987) have proposed a theoretical model to explain double peaks in the plasma concentration time profile for cimetidine when the drug is given in the fasted state. Central to the model proposed by these authors is the theory that increased motility in phase 3 of the migrating myoelectric complex leads to an increased rate of outflow from the stomach. According to the model, a double peak would result if the first part of the dose of a drug given in solution emptied exponentially and the residual volume emptied during phase 3. Studies carried out in dogs lend some support to this contention, since emptying of large volumes (> 150ml) occurs exponentially, but emptying of the smaller volumes follows the strong peristaltic contractions during phase 3 (Gupta et al., 1986).

Intestinal reserve length

It is widely appreciated that the main site of absorption is the proximal and mid-small intestine since in the stomach the low surface area and impermeability to small molecules may be a problem and in the colon the smaller surface area and bacterial content of the lumen might be limiting. Hofmann et al. (1983) commented that "since in man the length of the small intestine is probably 300-400 cm, a length of 160-350 cm is available as a bacteria-free absorptive site, therefore every drug must be formulated in such a manner that it is largely absorbed in this length of intestine". This philosophy is similar to the ideas which gave rise to the intestinal reserve length model (Ho et al., 1983), in which the absorption process is modelled as a simple first order process with an exponential decrease in drug concentration along the length of the small intestine. The authors defined the intestinal reserve length as the distance over which 95% of the drug would be absorbed. Although the intestinal reserve length produces a useful guideline, it assumes that there is no variation in the absorptive capacity along the length of the small intestine and it ignores the role of the colon.

The colon has several important functions including a fundamental role in electrolyte and water homeostasis. Mixing or "shuttling" activity, apparent in the ascending and transverse colon, may facilitate maximal exchange between the lumenal contents and the mucosa and may also contribute to prolonged transit times encountered in the colon compared other parts of the gastrointestinal tract. The nature of the lumenal contents varies through fluid in the ascending colon, becoming a semi-solid in the transverse colon and a solid in the descending colon. The fluid milieu of the ascending colon provides an opportunity for the absorption of drugs from sustained release dosage forms as noted for oxprenolol delivered in an osmotically-driven 'Oros' zero-order delivery system (Oros, Alza Corporation U.S.A). Figure 8 shows the plasma oxprenolol concentration and gastrointestinal transit data reported by Davis et al. (1988b). It was found that the extended plateau concentration corresponded to a residence of the unit in the colon, indicating the importance of this region of the gastrointestinal tract for drug absorption.

Marked differences have been shown in the transit of particulate and single unit dosage forms through the ascending bowel (Hardy et al., 1985). Small pellets were found to remain in the ascending colon whilst a single large unit was carried forward to the distal colon. The data provides the basis for the design of systems for delivery of drugs to the proximal colon.

owledgement
ndebted to the assistance of Dr N Washington, Ms P E Blackshaw, Ms
aves and Mrs K Steed in the preparation of this article.

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14

Deconvolution Techniques and their Use in Biopharmaceutics

Helga Möller

When assessing the performance of a pharmaceutical dosage form information on drug input can be obtained by means of a process known as deconvolution, providing the test system behaves in a linear manner.

Plasma concentrations and renal excretion profiles can be used as input and response functions for the calculation of input impulses. Equally, the input function can be assessed by deconvolution of pharmacological data such as desirable and undesirable physiological effects.

In this chapter, the absorption kinetics of indomethacin (taking account of reabsorption due to the enterohepatic circulation) are obtained by deconvolution of plasma concentrations, after oral and intravenous administration of a solution of the drug. The absorption of the drug from different regions of the intestine (duodenum, ileocaecal region and colon), as a function of time (including the longitudinal transport kinetics) is discussed by reference to the technique of gamma scintigraphy.

From this knowledge of the gastrointestinal absorption kinetics and the longitudinal transport kinetics of indomethacin it is then possible, by deconvolution of plasma concentrations, to assess the in vivo release of

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4

Small Intestine Transit

S S Davis

In man, the small intestine is that region between the stomach and the large bowel and comprises the three regions known as the duodenum, jejunum and ileum. Its total length is approximately 6 m, this being divided up into those three major regions as follows; duodenum 30 cm, jejunum 2.4 m, ileum 3.6 m. The major function of the small intestine is one of absorption of digested nutrients. For this reason, the intestinal lumen has numerous folds and projections to include villi and microvilli. This provides a very large surface area for the efficient uptake of solutes. The small intestine is also an important site for the absorption of pharmacological agents. This is especially so if the drug in question is released rapidly from its dosage form. However, if the drug is poorly soluble or is in the form of a controlled release dosage form, significant absorption of the drug may occur in the large bowel.

Ho and others (1983) have considered in detail the question of absorption versus transit in the small intestine by means of their reserve length concept. The assumption in their analysis was that it was necessary for the drug to be absorbed solely from the small intestine. If the drug were rapidly absorbed in the upper regions of the small intestine, then there would be a large reserve length. However, if the drug were poorly absorbed, then a longer period and hence transit would be required and the reserve length would be much smaller. For the case where the drug was not totally absorbed within the small intestine, the reserve length would be negative. This approach has been found useful for predicting the absorption characteristics and resultant bioavailability of drugs and drug projects.

he role of gastric emptying also needs to be appreciated for controlled
e systems, especially if they take the form of a large single unit. Such
em can be held for a long period of time within the stomach, because
size and the presence of food (Davis, 1987). Nevertheless the drug
sed into the gastric environment (either in solution or as small par-
) will be able to empty through the (constricted) pylorus into the small
tine. In this situation, the whole length of the small intestine will be
able for subsequent absorption so long as the intact dosage form
ins in the stomach. In other situations, especially where a dosage form
ministered to a fasted or lightly fed stomach, the system may pass into
mall intestine after only a few minutes. Its transit through the small
stine may then have a critical bearing upon the resultant bioavailability
e drug, especially if the compound is little absorbed within the colonic
ons or if an absorption "window" exists. Consequently, it is of impor-
e to have knowledge about the gastrointestinal transit of pharmaceuti-
dosage forms and especially their residence times within the small
stine. Surprisingly, until recently, the pharmaceutical literature con-
ed little real information on small intestinal transit time. Anecdotal
ures of 8 hours or longer appear to have no direct experimental basis
avis et al., 1986a). Work conducted at Nottingham and elsewhere has
w shown that the small intestinal transit of a variety of pharmaceutical
sage forms is usually from about 2-6 hours but can be as short as 1 hour.

OTILITY OF THE SMALL INTESTINE

As with gastric emptying, it is first of all important to establish whether
fasted or fed situation is being considered. If the subject is in a fasted or
terdigestive mode, then the small intestinal transit of a pharmaceutical
osage form (non-digestible system) will be influenced by phase 3 of the
igrating myoelectric complex (MMC) (Code and Marlett, 1975). As has
een discussed elsewhere in this book, this complex involving contractions
f different magnitude, will cause non-digestible material to be 'swept'
hrough the open pylorus and through the small intestine. In man, this
novement of material will continue into the terminal ileum. (In dogs, the
MMC is thought to pass through the ileocaecal sphincter). Thus it is to be
xpected that the small intestinal transit of a pharmaceutical dosage form
moving under the effect of the MMC from pylorus to the ileocaecal region
will take approximately 1.5-2 hours (Davis et al., 1986a).

In the fed state, the small intestine has two different motility patterns. First, there is a process of segmentation, where contractions within the small intestine cause some degree of mixing and no doubt allow close contact between digested nutrients and the mucosal surface thereby aiding absorption. A second process of peristalsis, involving coordinated muscular contractions, causes the food material to move in an aboral direction. Information on flow within the small intestine has been reviewed by Ho and others (1983) and the important points are summarised in Table 1.

Table 1 - Survey of Transit Times and Flow Velocities in Human Small Intestine (after Ho et al., 1983).

Method	Region transit time (min)	Mean velocity (cm/min)	Flow
perfused intubated small intestine -PEG - 400	jejunum (100 cm) ileum (100 cm)	30.7 18.6	3.26 5.38
pulmonary H_2 - excretion	small intestine	72.6	4.13
x-ray -barium sulphate suspension	small intestine	126	2.38
gamma scintigraphy -pellets	small intestine	156-228*	1.30-1.90*

*depending on density

MEASUREMENT OF GASTROINTESTINAL TRANSIT

A variety of methods can be used to determine the gastrointestinal transit of foodstuffs and more particularly, pharmaceutical dosage forms. In early studies, radiography was used (Bertrand et al., 1980). A dosage system material was rendered radiopaque (for example by inclusion of barium sulphate) and then a series of x-rays was taken in order to monitor the transit of the dosage form through the different regions of the small intestine. Today such studies would be considered to be hazardous and unethical.

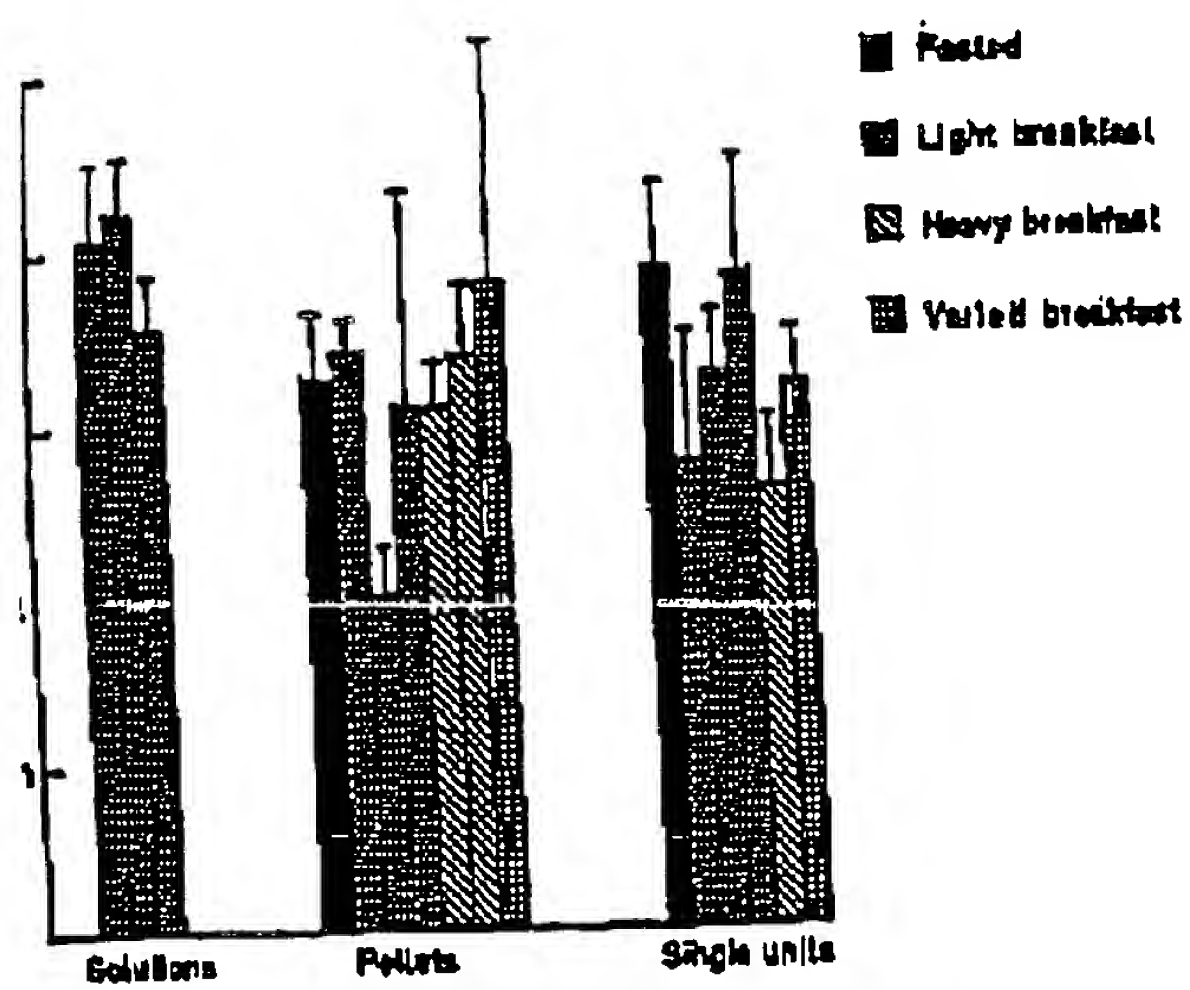
ormation on mouth to colon transit can be gained by the hydrogen
test (or variations thereof measuring labelled carbon dioxide)
ack *et al.*, 1982). This test relies upon the metabolism of certain
ydrate materials (e.g. lactulose) by the microbial flora within the
1. By generating gas which can be detected in the expired air, it is
e to make some estimation about the initial arrival of the admini-
naterial within the colon. This technique has been described in more
n the chapter by Read and colleagues. Good correlation with other
ues such as scintigraphy have been claimed. It is important in such
gations to ensure that the administered material does not create
c effects that may cause underestimation of transit times. Further-
in some subjects, bacterial overgrowth into the terminal ileum will
premature metabolism of the administered marker, thereby also
an underestimate.
adiotelemetry capsules, that can provide a continuous recording of
intestinal pH, can be employed to monitor small intestinal transit
s *et al.*, 1988). The characteristic rise in pH as the capsule enters the
num is taken as the starting point. The smaller, but equally charac-
c change in pH as the device passes through the ileocaecal sphincter
caecum can be used as the end point. This change in pH is normally
rather than the rise that has often been suggested in the pharmaceutical
ure. The radiotelemetry technique can over-estimate small intestinal
t time because, as will be discussed below, it is not unusual for large
units to undergo periods of stagnation within the terminal ileum
e they are passed into the caecum. Thus the device could have
lled through the whole of the small intestine within a short period of
but may then have remained at the ileocaecal junction for a period of
s before a significant fall in pH was observed.
Studies at Nottingham have employed the technique of gamma scinti-
hy in order to evaluate small intestinal transit. In the scintigraphic
od, the pharmaceutical dosage form is labelled with a small amount of
itable gamma emitting radionuclide (technetium-99m or indium-111)
the transit of the material followed using a conventional gamma
era. This technique is not particularly useful in defining anatomical
il, certainly so far as the small intestine is concerned, and unlike
ography, it is not possible normally to delineate loops or anatomical
ures in the small intestine. However, the presence of the dosage form
he stomach and its gastric emptying can be well defined. Its arrival in
ileocaecal region is also easy to assess. Thus it is possible to evaluate
all intestinal transit time by difference. For a single unit system, small
estinal transit time is taken as the difference in time on leaving the
mach and arriving in the ileocaecal region. For a pellet system, which

may well empty from the ...
especially when administered with food, then it is normal practice to take
the time for 50% gastric emptying and the time for 50% colonic filling and
to use the difference between these two numbers as a time for small
intestinal transit. For more sophisticated studies, particularly when inves-
tigating drug related effects, it is possible to examine the various deciles, i.e.
80% stomach, 20% small intestine; through to 10% stomach, 90% small
intestine.

Kaus *et al.* (1984) have employed three dimensional imaging in order
to define the passage of a dosage form through the different regions of the
small intestine. This interesting approach was able to show that the transit
rate was of the order of 4.2-5.6 cm per minute, however, it was not possible
to measure transit through the duodenum because this occurred so rapidly
(in less than 5 minutes). Unfortunately this technique is extremely tedious
to perform and has not been suitable for routine studies on volunteers and
patients.

SMALL INTESTINAL TRANSIT OF PHARMACEUTICAL DOSAGE FORMS

During the last five years, the Nottingham Group has undertaken
various transit studies on a large number of volunteers and to a lesser extent
with patients. In 1986 an analysis of all the then available data showed con-
clusively that mean small intestinal transit time was of the order of 3-4 hours
with a standard deviation of 1 hour (Davis *et al.*, 1986a) (Figure 1). This
mean transit time is much less than had been hitherto proposed and is
apparently little or unaffected by differences in gastric emptying. It was
found that the small intestinal transit time for solutions, pellets and single
units is not statistically different for both the fasted and fed states. Further-
more, there were no significant differences that could be attributed to age,
or pathological conditions such as ulcerative colitis, diarrhoea or constipa-
tion. Recently, Mundy *et al.* (1989) have studied the effect of eating on
transit through the small intestine. Subjects either remained fasting after
dosing or consumed a meal at different times after dosing. The mean small
intestinal transit times in 8 subjects were not significantly different.
Additionally it has been shown that transit rates are unaffected by exercise
(Ollerenshaw *et al.*, 1987). The transit of dosage forms through the small
intestine appears to be more or less independent of input (gastric emptying)
or to output (filling of the colon and by inference bowel habits). Interest-
ingly, the mean figure of 3 hours obtained by Davis *et al.* (1986a) is similar
to that obtained by Malagelada *et al.* (1984) for radiolabelled foodstuffs.



e 1 - Small intestine transit of dosage forms following their administration after fasts of different calorific values (after Davis et al., 1986a).

s it can be concluded that the apparently rapid transit of pharmaceutical age forms through the small intestine is not so surprising as it would n. It simply reflects normal physiological function! Occasionally viduals have been seen who have small intestinal transit times greater 6 hours, and some individuals have small intestinal transit times of 1 r or less.

reading of Multiparticulate Systems

While gastric emptying will not affect the mean transit time of a dosage m through the small intestine to any great extent, it will affect the reading of a multiparticulate system within this region. If a multi-unit llet (or for that matter small tablet) system is administered together with soon after a meal, then the individual units will be well mixed with the od. If the unit size is smaller than approximately 7 mm, they are able to npty through the partially constricted pyloric sphincter into the small testine together with digested food during the digestive state (Khosla et l., 1989). Consequently, it is to be expected that the emptying and preading of pellets (and similar multi-unit systems) will be very dependent

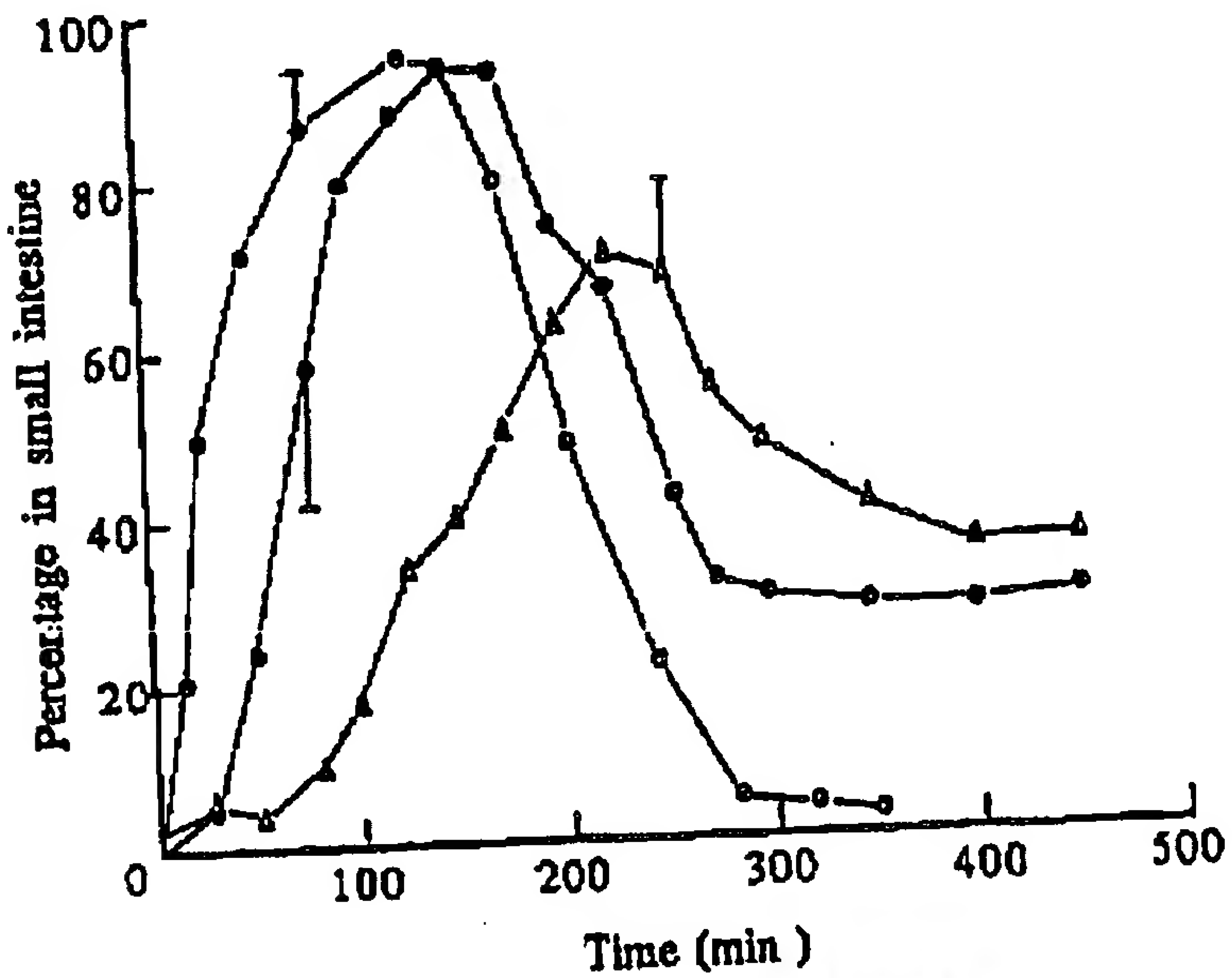
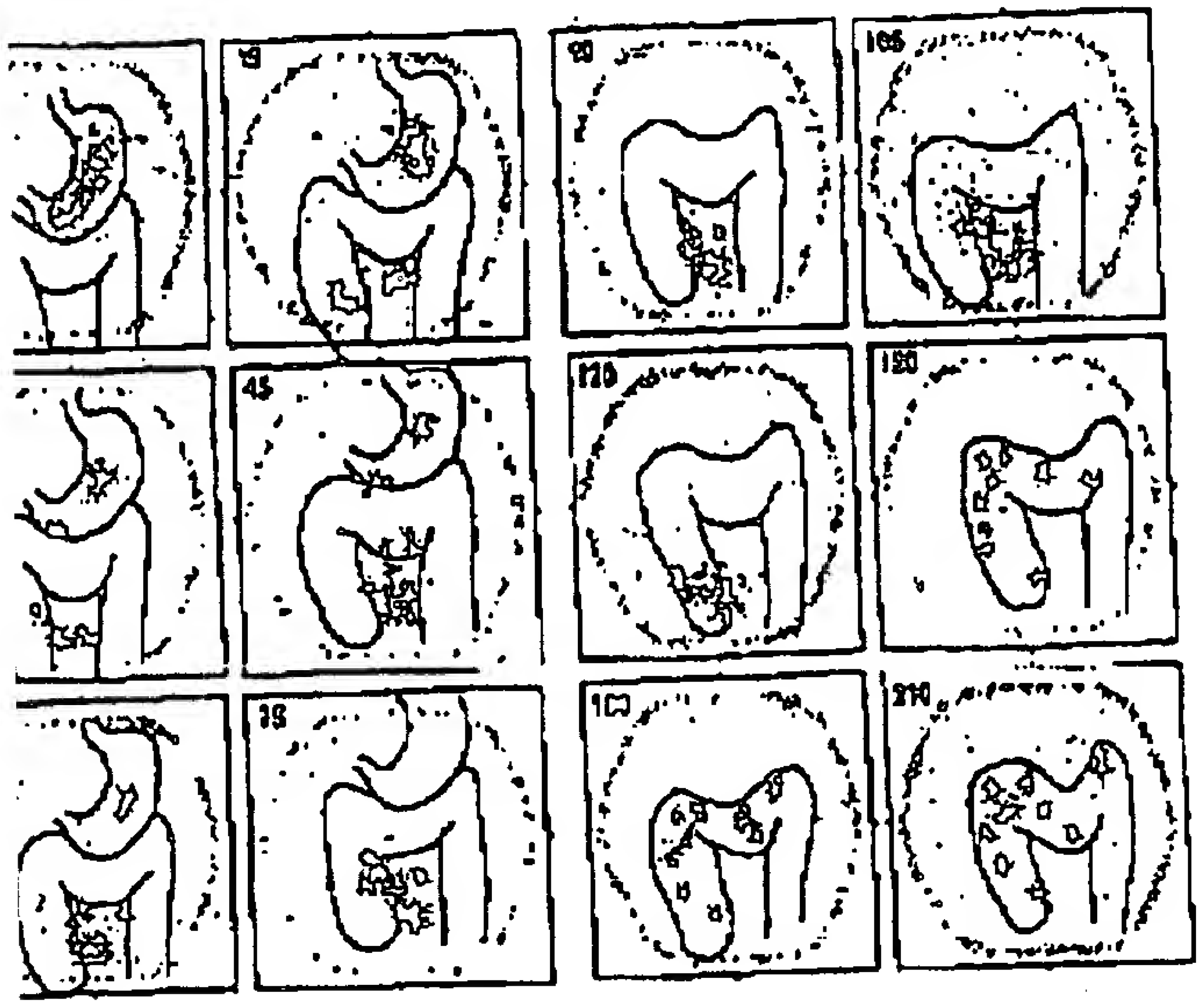


Figure 2 - Small intestine transit of pellets following their administration after breakfasts of different calorific values (o fasted; • light breakfast; Δ heavy breakfast).

upon the calorific load of the administered meal. For example, if pellets are given with a light meal, they will empty into the small intestine quite rapidly and there will only be a small degree of spreading. In comparison, if the pellets are given with a heavy meal, they will be emptied more slowly, be dispersed within the food mass and have good spreading within the small intestine (Figure 2). While meal size itself is also expected to have some effect on small intestinal transit, this effect has not yet been demonstrated in the Nottingham studies.

The Role of the Ileocaecal Sphincter

The spreading of a multiparticulate system through the small intestine due to the effect of gastric emptying, does not necessarily mean that the system will remain in a spread state throughout the whole of the gastrointestinal tract. It is quite usual to see the re-grouping of a multiparticulate system as the material reaches the ileocaecal sphincter (Figure 3). As discussed by Phillips elsewhere in this book, the ileocaecal sphincter appears to have a regulatory function in controlling the movement of food



o 3 - Gastrointestinal transit of 10 x 4 mm tablets administered to a healthy individual
a light breakfast (after Khosla *et al.*, 1989).

the small intestine into the large intestine (and also in preventing reflux
e large intestinal contents into the small intestine). This re-grouping
omenon is normally followed by a further spreading of the individual
within different regions of the colon.

A related phenomenon is the stagnation or "hold-up" of large single
s in the ileocaecal region. If the ileocaecal sphincter acts as some form
alve (Phillips *et al.*, 1988) then it is to be expected that large single units
y be held in the terminal ileum for extended periods of time. In studies
young and elderly volunteers, it has been found that the period of time a
ge single unit controlled release tablet remained in the ileocaecal region
ried from 2-10 hours (Figure 4). Recently, Marvola *et al.* (1987) using
ay methods, have reported stagnation times ranging from 2-20 hours in
ileocaecal region. No information is available about the stagnation of
ge single units in the terminal ileum for elderly patients, especially those
ith constrictions and diverticulosis

harmaceutical Factors

A range of pharmaceutical factors has been examined in Nottingham

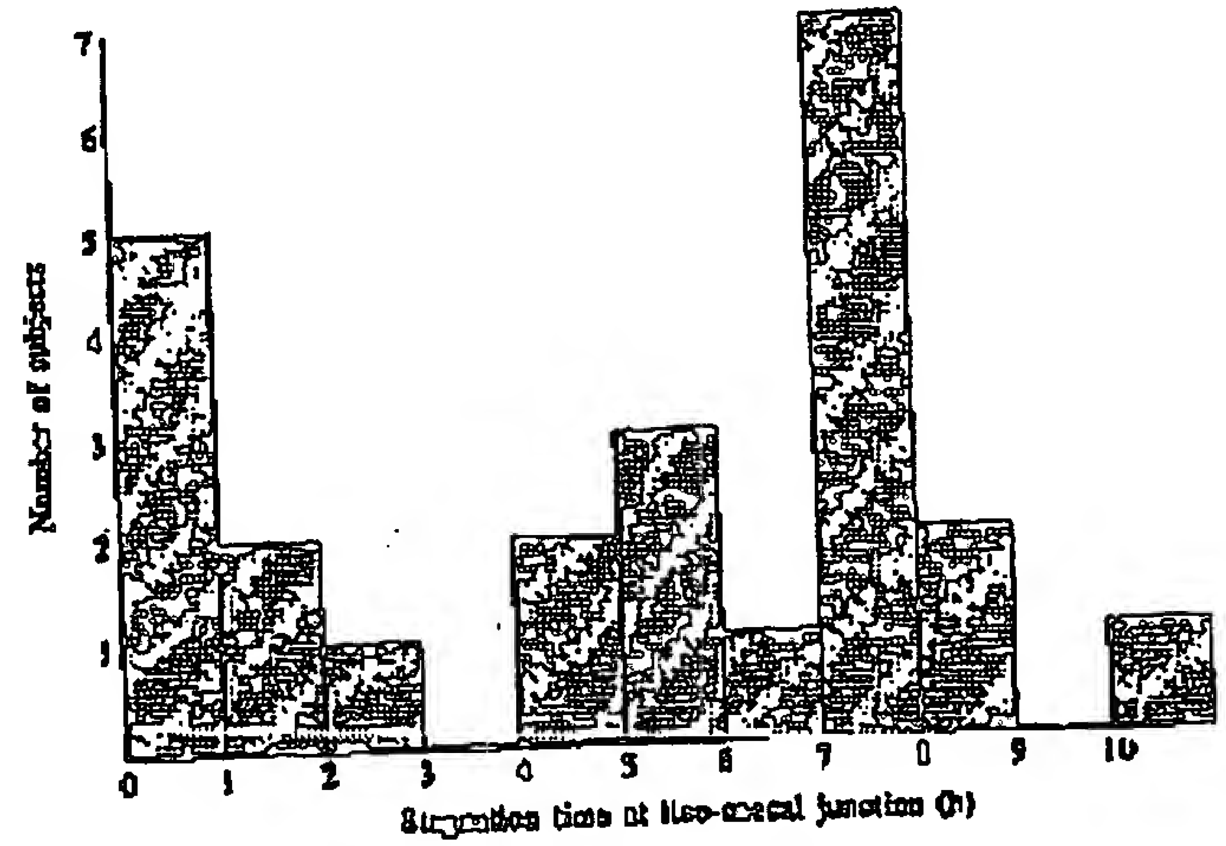


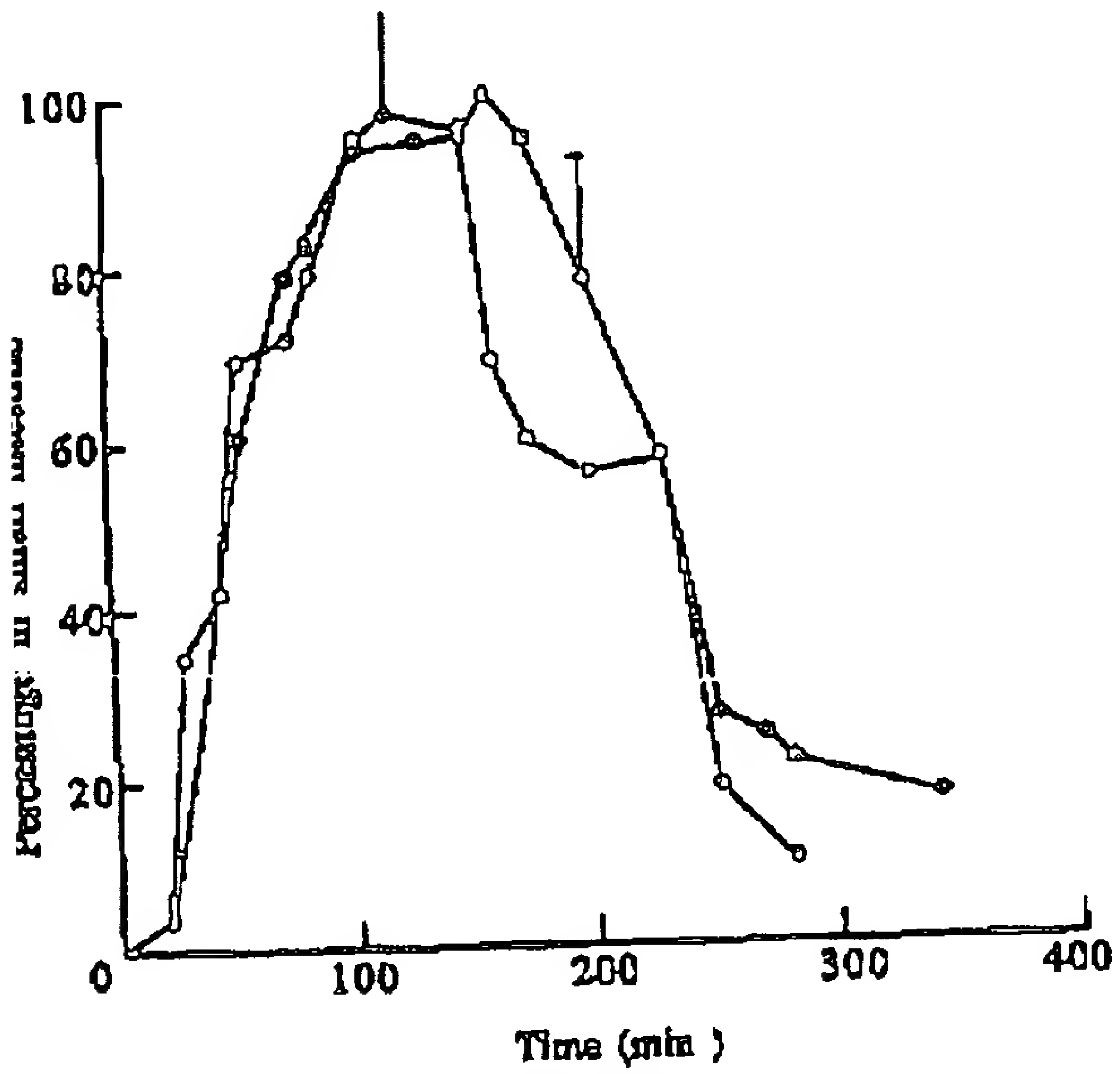
Figure 4 - Stagnation of large single unit matrix systems in the ileocaecal region.

to investigate whether these might affect gastric emptying and small intestinal transit. These have included physiological variables such as age, time of dosage administration, body position, exercise, bed-rest (Khosla and Davis, 1986). In none of these studies were large differences in small intestinal transit time observed. Indeed, as discussed above, small intestinal transit is relatively consistent, certainly when compared to transit in the large bowel and gastric emptying.

Small intestinal transit (and gastric emptying) can be modified significantly by the presence of unabsorbed fat or protein hydrolysate within the terminal ileum. Studies by Welch *et al.*, (1988) have suggested that apparently there are receptors in the terminal ileum that can assess the efficiency of the absorption process so far as nutrients are concerned. If the absorption process is inefficient, then the ileal "braking mechanism" comes into play, thereby providing a longer period of time for food to remain within the small bowel for absorption to occur.

PHARMACEUTICAL STRATEGIES

Considerable advantage may well accrue if a pharmaceutical dosage form could be retained for a longer period of time within the stomach and the small intestine, particularly if the drug to be delivered is poorly absorbed in the colon. Furthermore, with some drugs it has been proposed that they have an absorption "window" somewhere in the small intestine and as a



...e 5 - The effect of a putative bioadhesive on the transit of pellets in the small intestine ...ated; o formulated with polycarbophil.

sequence, once the dosage form or undissolved drug has passed the ...dow", then the absorption will fall off dramatically (Houston and ...od, 1980). Unfortunately, attempts to demonstrate the utility of various ...maceutical strategies to alter gastric emptying and small intestinal ...sit times have not been very successful when undertaken in healthy ...nan volunteers. Studies in Nottingham have demonstrated that putative ...adhesive systems (Khosla and Davis, 1987) and dosage forms with low ...l high density have little or no effect on small intestinal transit (Davis *et* ..., 1986b) (Figure 5). This does not mean to say that other approaches for ...adhesion and modification of small intestinal transit time may not be ...ccessful in the future, but at the present time the available data do not hold ...ly promise.

...harmacokinetics

Elsewhere in this book the inter-relationship between transit data and ...harmacokinetics has been evaluated. However, it is interesting to show ...ne example for a controlled release pellet system of isosorbide mononi-

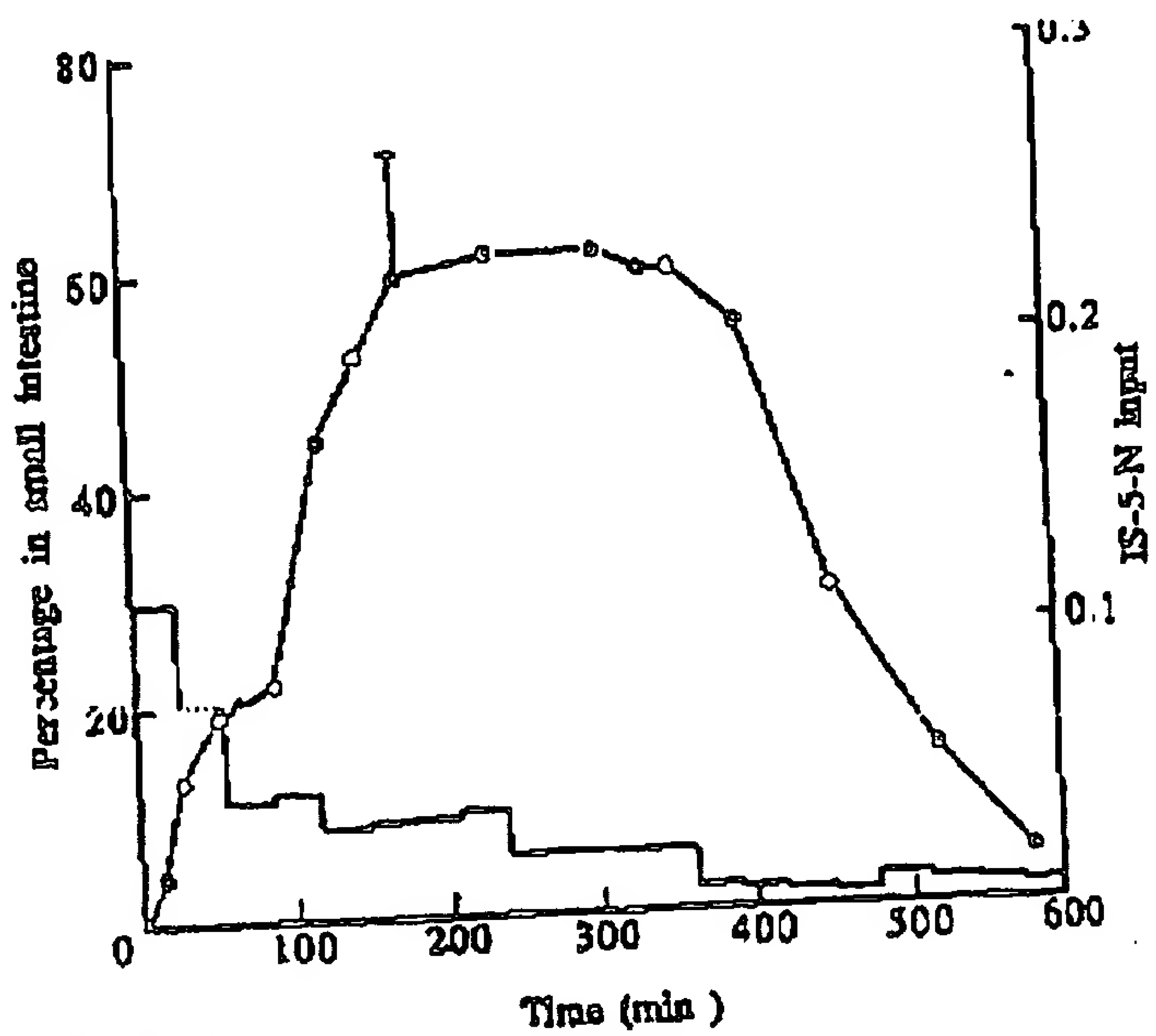


Figure 6 - Relation between the small intestine transit of controlled release pellets of isosorbide-5-nitrate (IS-5-N) and drug input expressed □ the fraction of the total released (after Fischer et al., 1987).

trate. This drug is better absorbed in the small intestine than in the colon and Fischer *et al.*, (1987) have shown that drug input, measured by deconvo-lution of pharmacokinetic data, can be well related to the transit of the dosage form through the small intestinal regions (Figure 6). The fall in drug input coincided well with the bulk of the pellet system arriving in the colon.

CONCLUSION

The transit of a pharmaceutical dosage form through the small intestine can be measured by the non-invasive technique of gamma scintigraphy. In healthy volunteers (and apparently in patients), small intestinal transit time is of the order of about 3 hours. This short transit time has implications for the design and evaluation of controlled release systems. If a dosage form is given to a fasted individual, then it is quite possible for the product to reach the terminal ileum within 3 hours or less. If the drug is not well absorbed in the colon then the bioavailability of the drug will be predictably poor.

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